09/937,009

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     (FILE 'HOME' ENTERED AT 10:08:25 ON 28 JUL 2006)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 10:08:53 ON 28 JUL 2006
L1         67106 S PHOSPHOINOSITIDE
L2         19704 S L1 (2W) KINASE##
L3          2205 S PDK1
L4         20665 S L2 OR L3
L5           319 S PRK2
L6            60 S L4 AND L5
L7            27 DUP REM L6 (33 DUPLICATES REMOVED)
L8            12 S L5 AND PIF
L9             3 DUP REM L8 (9 DUPLICATES REMOVED)
L10          346 S PKC (W)RELATED
L11           43 S L5 AND L10
L12           31 DUP REM L11 (12 DUPLICATES REMOVED)
L13           18 S PDK2 AND L5
L14            8 DUP REM L13 (10 DUPLICATES REMOVED)
L15         1023 S PKB (W)ACTIVAT?
L16           72 S L3 AND L15
L17           19 DUP REM L16 (53 DUPLICATES REMOVED)
L18            0 S L5 AND L15
L19          248 S L4 AND L15
L20         1092 S SER473
L21           43 S L19 AND L20
L22           15 DUP REM L21 (28 DUPLICATES REMOVED)
               E ALESSI D/AU
L23          138 S E3
               E BALENDRAN A/AU
L24           47 S E3-E6
               E DEAK M/AU
L25          194 S E3
               E CURRIE R/AU
L26          105 S E3
               E DOWNES P/AU
L27           30 S E3
               E CASAMAYOR A/AU
L28          111 S E3
L29          496 S L23 OR L24 OR L25 OR L26 OR L27
L30            5 S L7 AND L29
L31            5 DUP REM L30 (0 DUPLICATES REMOVED)

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 NEWS  6  MAY 11   KOREAPAT updates resume
 NEWS  7  MAY 19   Derwent World Patents Index to be reloaded and enhanced
 NEWS  8  MAY 30   IPC 8 Rolled-up Core codes added to CA/CAplus and
                   USPATFULL/USPAT2
 NEWS  9  MAY 30   The F-Term thesaurus is now available in CA/CAplus
 NEWS 10  JUN 02   The first reclassification of IPC codes now complete in
                   INPADOC
 NEWS 11  JUN 26   TULSA/TULSA2 reloaded and enhanced with new search and
                   and display fields
 NEWS 12  JUN 28   Price changes in full-text patent databases EPFULL and PCTFULL
 NEWS 13  JUl 11   CHEMSAFE reloaded and enhanced
 NEWS 14  JUl 14   FSTA enhanced with Japanese patents
 NEWS 15  JUl 19   Coverage of Research Disclosure reinstated in DWPI

 NEWS EXPRESS  JUNE 30 CURRENT WINDOWS VERSION IS V8.01b, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.

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=> file medline embase biosis biotechds scisearch hcaplus ntis lifesci
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                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

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FILE 'HCAPLUS' ENTERED AT 10:08:53 ON 28 JUL 2006
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FILE 'LIFESCI' ENTERED AT 10:08:53 ON 28 JUL 2006
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=> s phosphoinositide
L1        67106 PHOSPHOINOSITIDE

=> s l1 (2w) kinase##
L2        19704 L1 (2W) KINASE##

=> s PDK1
L3         2205 PDK1

=> s l2 or l3
L4        20665 L2 OR L3

=> s PRK2
L5          319 PRK2

=> s l4 and l5
L6           60 L4 AND L5

=> dup rem l6
PROCESSING COMPLETED FOR L6
L7            27 DUP REM L6 (33 DUPLICATES REMOVED)

=> d 1-27 ibib ab

L7   ANSWER 1 OF 27  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2006:318918  HCAPLUS
DOCUMENT NUMBER:          144:343640
TITLE:                    Resorcylic acid lactone kinase inhibitors, and their
                          therapeutic use for the treatment of cancers and other
                          conditions
INVENTOR(S):              Santi, Daniel V.; Reid, Ralph C.; Hutchinson, Richard
                          C.; Sundermann, Kurt F.; Lau, Janice
PATENT ASSIGNEE(S):       Kosan Biosciences Incorporated, USA
SOURCE:                   PCT Int. Appl., 110 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
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PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2006036941	A2	20060406	WO 2005-US34537		20050926
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
US 2006079494	A1	20060413	US 2005-236244		20050926
PRIORITY APPLN. INFO.:			US 2004-613680P	P	20040927
			US 2004-629575P	P	20041118
			US 2005-698520P	P	20050711

OTHER SOURCE(S): MARPAT 144:343640

AB Resorcylic acid lactones having a C5-C6 cis double bond and a ketone at C7 and other compds. capable of Michael adduct formation are potent and stable inhibitors of a subset of protein kinases having a specific cysteine residue in the ATP binding site. Compds. of the invention include e.g. hypothemycin. Compound preparation is included.

L7 ANSWER 2 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:152715 HCAPLUS

DOCUMENT NUMBER: 144:233089

TITLE: Preparation of aryl-amino substituted pyrrolopyrimidine multi-kinase inhibiting compounds as antiproliferative, particularly antitumor agents

INVENTOR(S): Ahmed, Saleh; Barba, Oscar; Bloxham, Jason; Dawson, Graham; Gattrell, William; Kitchin, John; Pegg, Neil Anthony; Saba, Imaad; Shadiq, Shazia; Smith, Colin Peter Sambrook; Smyth, Don; Steinig, Arno G.; Wilkes, Robin; Foreman, Kenneth; Weng, Qinghua Felix; Stolz, Kathryn; Tavares, Paula; Panicker, Bijoy; Li, An-Hu; Dong, Hanqing; Ma, Lifu; Cox, Matthew

PATENT ASSIGNEE(S): Osi Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 253 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006017443	A2	20060216	WO 2005-US27274	20050801
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

PRIORITY APPLN. INFO.: US 2004-598173P P 20040802
US 2005-698516P P 20050712

OTHER SOURCE(S): MARPAT 144:233089

AB Title compds. I [X = N, C-CN; A = 1,4-piperidinylene, 1,4-pyrazinylene, 1,2,3,6-tetrahydro-1,4-pyridinylene, etc.; Z = (un)substituted hetaryl, alkyloxyalkyl, alkylsulfonyl, dialkylamino, hetarylsulfonyl, etc.; Y = O, S, -N(alkyl)-, etc.; R1 = (un)substituted het-aryl, heterocyclyl; and their stereoisomers, and their pharmaceutically acceptable salts] were prepared as inhibitors of least two of the Abl, Aurora-A, Blk, c-Raf, cSRC, Src, PRK2, FGFR3, Flt3, Lck, Mekl, PDK-1, GSK3β, EGFR, p70S6K, BMX, SGK, CaMKII, Tie-2, IGF-1R, Ron, Ret, and KDR kinases in animals, including humans, for the treatment and/or prevention of various diseases and conditions such as cancer. For example, Pd-coupling of (1H-indazol-5-yl)(6-iodo-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amine with [1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-4-yl]boronic acid gave pyrrolopyrimidine II. In kinase inhibition studies, selected I inhibited at least 2 of the Abl, Aurora-A, Blk, c-Raf, cSRC, Src, PRK2, FGFR3, Flt3, Lck, Mek1, PDK-1, GSK3β, EGFR, p70S6K, BMX, SGK,CaMKII, Tie-2, Ret and KDR kinases at an IC50 of greater than 50% inhibition at 10 to 14 nM.

L7 ANSWER 3 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1314312 HCAPLUS
DOCUMENT NUMBER: 144:68264
TITLE: Minimal common regions in chromosomes showing changes in copy number in cancers and their use in the diagnosis, prevention, and treatment
INVENTOR(S): Chin, Lynda
PATENT ASSIGNEE(S): Dana-Farber Cancer Institute, Inc., USA
SOURCE: PCT Int. Appl., 152 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005118869	A2	20051215	WO 2005-US18850	20050527

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-575795P P 20040528
US 2004-580337P P 20040615

AB Small chromosomal regions, minimal common regions (MCRs) that show a change in copy number in neoplastic tissue are identified for use in the early diagnosis of cancer and as markers in the prevention and treatment of the disease.

L7 ANSWER 4 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1289100 HCAPLUS
DOCUMENT NUMBER: 144:36367
TITLE: Preparation of 2-substituted 4-thiazolylpyrimidines as protein kinase inhibitors with improved solubility properties

INVENTOR(S): Wang, Shudong; Wood, Gavin; Duncan, Kenneth; Meades, Christopher; Gibson, Darron; Mclachlan, Janice; Fischer, Peter
PATENT ASSIGNEE(S): Cyclacel Limited, UK
SOURCE: PCT Int. Appl., 216 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005116025	A2	20051208	WO 2005-GB2134	20050526
WO 2005116025	A3	20060223		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2004-11791 A 20040526
OTHER SOURCE(S): MARPAT 144:36367

AB The present invention relates to 2-substituted 4-thiazolylpyrimidines (shown as I; variables defined below; e.g. (3-methylsulfonylphenyl)[4-(4-methyl-2-methylaminothiazol-5-yl)pyrimidin-2-yl]amine (shown as II)), their preparation, pharmaceutical compns. containing them and their use as inhibitors of ≥1 protein kinases, and hence their use in the treatment of proliferative disorders, viral disorders and/or other disorders. For I: 1 of X1 and X2 is S, and the other is N; Z is NH, NHCO, NHCOCH2, NHSO2, NHCH2, CH2, CH2CH2, CH:CH, O, S, SO2, or SO; R1, R2, R3, R4, R5, R6, R7 and R8 = H, alkyl, alkyl-R9, aryl, aryl-R9, aralkyl, aralkyl-R9, halo, et al. or two of R4-R8 are linked to form a cyclic ether containing ≥1 oxygens; R9 = solubilizing group = mono, di- or polyhydroxylated alicyclic, di- or polyhydroxylated aliphatic or aromatic, carbohydrate derivative, O- and/or S-containing heterocyclic group, et al.; addnl. details including provisos are given in the claims. Protein kinase inhibition properties of many I for many kinases are tabulated. Although the methods of preparation are not claimed, prepns. and/or characterization data for 220 examples of I are included. For example, [4-(2-tert-butylamino-4-methylthiazol-5-yl)pyrimidin-2-yl](4-methyl-3-nitrophenyl)amine was prepared by condensation of 1-(2-tert-butylamino-4-methylthiazol-5-yl)-3-dimethylaminopropenone and N-(4-methyl-3-nitrophenyl)guanidine nitrate. Compds. I are also claimed useful in an assay for identifying further candidate compds. capable of inhibiting various enzymes.

L7 ANSWER 5 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1125605 HCAPLUS
DOCUMENT NUMBER: 143:400850
TITLE: Diagnosing depression by analyzing expression profiles of marker genes
INVENTOR(S): Rokutan, Kazuhito; Ohmori, Tetsuro; Morita, Kyoko; Ohta, Masayuki; Saito, Toshiro
PATENT ASSIGNEE(S): Hitachi Ltd., Japan
SOURCE: Eur. Pat. Appl., 61 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
EP 1586657	A1	20051019	EP 2005-6769		20050329
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU					
JP 2005312435	A2	20051110	JP 2005-42534		20050218
US 2005239110	A1	20051027	US 2005-91674		20050329
PRIORITY APPLN. INFO.:			JP 2004-96068	A	20040329
			JP 2005-42534	A	20050218

AB The present invention relates to a method of diagnosing depression, wherein gene expression is analyzed using mRNA of patients' peripheral bloods to cluster patients afflicted with depression, and conditions thereof are then diagnosed. The present inventors have focused on peripheral leukocytes that can be easily obtained as specimens and allow many receptors of factors associated with stress responses to be expressed therein in order to objectively diagnose the conditions of depression, in the development of which stress plays an important role. They have extensively analyzed the expression patterns of mRNAs of approx. 1,500 genes associated with stress responses and then developed certain patterns. Thus, they have found a method that is capable of classification patients afflicted with depression and diagnosing the conditions thereof. More specifically, the present invention relates to a method of diagnosing depression, wherein gene expression is analyzed using mRNA of a subject's peripheral blood to evaluate whether or not the subject is afflicted with depression, the type of depression of a subject who had been evaluated as being afflicted with depression is identified, and the conditions of depression are then diagnosed in accordance with the type of depression. According to this method, the expression profiles of the marker gene for depression (an indicator for evaluating whether or not a subject has been afflicted with depression) selected from among the genes listed in Table 1 can be employed to evaluate whether or not a subject is afflicted with depression. When a subject was evaluated as being afflicted with depression, the expression profiles of the marker gene for classification (an indicator for classifying a patient afflicted with depression) selected from among the genes listed in Table 2 can be employed to identify the type of depression in the subject to be type PA or PB. The present inventors extracted RNA from the whole blood collected from patients and healthy volunteers as described below, and gene expression of patients was then analyzed using DNA chips, along with that of healthy volunteers. The marker genes were determined based on the results.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:1059119 HCAPLUS
DOCUMENT NUMBER: 142:32932
TITLE: Combination therapy for cancer and other proliferative disorders
INVENTOR(S): Blatt, Lawrence M.; Seiwert, Scott D.; Ozes, Osman N.
PATENT ASSIGNEE(S): Intermune, Inc., USA
SOURCE: PCT Int. Appl., 635 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2004105684	A2	20041209	WO 2004-US15346	20040513

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:	US 2003-471841P	P	20030516
	US 2003-485474P	P	20030708
	US 2003-511259P	P	20031014
	US 2003-511280P	P	20031014
	US 2003-511415P	P	20031014
	US 2003-514173P	P	20031024
	US 2004-561940P	P	20040413

AB The invention provides methods of treating proliferative disorders, including angiogenesis-mediated disorders, cancer, and fibrotic disorders. In some embodiments, the methods involve administering a Type II interferon receptor agonist and a Type I interferon receptor agonist. In other embodiments, the methods involve administering a Type II interferon receptor agonist, a stress-activated protein kinase (SAPK) inhibitor, and a third therapeutic agent. In other embodiments, the methods involve administering a Type II interferon receptor agonist and a vascular endothelial growth factor (VEGF) antagonist. In other embodiments, the methods involve administering a VEGF antagonist and a SAPK inhibitor. The invention further provides methods of treating fibrotic disorders. In some embodiments, the methods involve administering a Type I interferon receptor agonist, a Type II interferon receptor agonist; and a tumor necrosis factor (TNF) antagonist. In other embodiments, the methods involve administering a Type II interferon receptor agonist and a TNF antagonist. In other embodiments, the methods involve administering pirfenidone or a pirfenidone analog and a TNF antagonist. In other embodiments, the methods involve administering a Type II interferon receptor agonist and a transforming growth factor-β (TGF-β) antagonist. In other embodiments, the methods involve administering a SAPK inhibitor alone or in combination with a Type II interferon receptor agonist. In other embodiments, the methods involve administering N-acetyl cysteine (NAC) and a SAPK inhibitor. In other embodiments, the methods involve administering NAC and a Type II interferon receptor agonist.

L7 ANSWER 7 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	2004:453193 HCAPLUS
DOCUMENT NUMBER:	141:23537
TITLE:	Preparation of 3,5-diamino[1,2,4]triazoles as protein kinase inhibitors
INVENTOR(S):	Pierce, Albert C.; Arnost, Michael; Davies, Robert J.; Forster, Cornelia J.; Galullo, Vincent; Grey, Ronald; Ledeboer, Mark; Tian, Shi-kai; Xu, Jinwang; Binch, Hayley; Ledford, Brian; Messersmith, David; Nanthakumar, Suganthi; Jayaraj, Andrew
PATENT ASSIGNEE(S):	Vertex Pharmaceuticals Incorporated, USA
SOURCE:	PCT Int. Appl., 392 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2004046120	A2	20040603	WO 2003-US36849	20031117
WO 2004046120	A3	20040812		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2505789	AA	20040603	CA 2003-2505789	20031117
AU 2003294329	A1	20040615	AU 2003-294329	20031117
US 2004214817	A1	20041028	US 2003-715111	20031117
EP 1562589	A2	20050817	EP 2003-789812	20031117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003016350	A	20050927	BR 2003-16350	20031117
CN 1738615	A	20060222	CN 2003-80108825	20031117
JP 2006515313	T2	20060525	JP 2004-570619	20031117
NO 2005002888	A	20050812	NO 2005-2888	20050610
PRIORITY APPLN. INFO.:			US 2002-426681P P	20021115
			US 2003-447705P P	20030211
			WO 2003-US36849 W	20031117

OTHER SOURCE(S): MARPAT 141:23537

AB Title compds. I [wherein R1 = H, YR'; Y = (un)substituted alkylidene wherein up to two methylene units are optionally and independently replaced with O, S, (un)substituted NH, OCO, CO2, CO; R' = independently H or (un)substituted aliphatic group, (hetero)cyclic ring; R2 = TnAr1, TnCy1; R3 = LmAr2, LmCy2; L, T = (un)substituted alkylidene wherein one methylene unit is optionally replaced by S, O, CS, CO2, OCO, CO, COCO, SO, SO2, PO, PO2, or (un)substituted NH, CONH, NHCO, NHCO2, SO2NH, NHSO2, CONHNH, NHCONH, OCONH, NHNH, NHSO2NH; m, n = 0-1; Ar1, Ar2 = (un)substituted mono- or bicyclic (hetero)aryl; Cy1, Cy2 = (un)substituted mono- or bicyclic aliphatic or heterocyclic ring; or NR1R2 = (un)substituted heterocycle; R4 = H, alkyl; with the proviso that when R5 = H, then R4 = H; R5 = H; or R3 and R5 taken together form an (un)substituted (hetero)cycle; and pharmaceutically acceptable salts thereof] were prepared as inhibitors of the protein kinases FLT-3, FMS, c-KIT, PDGFR, JAK, AGC sub-family, CDK, GSK, SRC, ROCK, and/or SYK (no data). For example, cycloaddn. of N-cyano-N'-(2-chloro-4-morpholinophenyl)-O-phenylisourea and 2-hydrazinopyridine in i-PrOH gave II (79%). The invention also provides pharmaceutical compns. comprising the compds. of the invention and methods of using the compns. in the treatment of various disorders, such as cancer, Alzheimer's disease, restenosis, angiogenesis, glomerulonephritis, cytomegalovirus, HIV, herpes, psoriasis, atherosclerosis, alopecia, an autoimmune disease, a viral infection, a neurodegenerative disorder, a disorder associated with thymocyte apoptosis, a proliferative disorder, or a hematopoietic disorder (no data).

L7 ANSWER 8 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	2004:371064 HCAPLUS
DOCUMENT NUMBER:	140:373461
TITLE:	Evaluation of breast cancer states and outcomes using gene expression profiles
INVENTOR(S):	West, Mike; Nevins, Joseph R.; Huang, Andrew
PATENT ASSIGNEE(S):	Synpac, Inc., USA; Duke University
SOURCE:	PCT Int. Appl., 799 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004037996	A2	20040506	WO 2003-US33656		20031024
WO 2004037996	A3	20041229			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2004083084	A1	20040429	US 2002-291878		20021112
WO 2004044839	A2	20040527	WO 2002-US38216		20021112
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2004106113	A1	20040603	US 2002-291886		20021112
AU 2003284880	A1	20040513	AU 2003-284880		20031024
PRIORITY APPLN. INFO.:			US 2002-420729P	P	20021024
			US 2002-421062P	P	20021025
			US 2002-421102P	P	20021025
			US 2002-424701P	P	20021108
			US 2002-424715P	P	20021108
			US 2002-424718P	P	20021108
			US 2002-291878	A	20021112
			US 2002-291886	A	20021112
			US 2002-425256P	P	20021112
			WO 2002-US38216	A	20021112
			WO 2002-US38222	A	20021112
			US 2003-448461P	P	20030221
			US 2003-448462P	P	20030221
			US 2003-457877P	P	20030327
			US 2003-458373P	P	20030331
			WO 2003-US33656	W	20031024

AB The present invention relates generally to a method for evaluating and/or predicting breast cancer states and outcomes by measuring gene and metagene expression levels and integrating such data with clin. risk factors. Genes and metagenes whose expressions are correlated with a particular breast cancer risk factor or phenotype are provided using binary prediction tree modeling. The invention provides 175 genes associated with metagene predictors of lymph node metastasis, 216 genes associated with metagene predictors of breast cancer recurrence, and 496 metagenes related to breast cancer study. Methods of using the subject genes and metagenes in diagnosis and treatment methods, as well as drug screening methods, etc are also provided. In addition, reagents, media and kits that find use in practicing the subject methods are also provided.

L7 ANSWER 9 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:355104 HCAPLUS
DOCUMENT NUMBER: 140:368628
TITLE: AGC protein kinase modulator identification assay
INVENTOR(S): Biondi, Richardo Miguel; Frodin, Morten; Antal, Torben

Laszio
PATENT ASSIGNEE(S): University Court of the University of Dundee, UK
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004035811	A2	20040429	WO 2003-GB4446	20031014
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003271951	A1	20040504	AU 2003-271951	20031014
PRIORITY APPLN. INFO.:			GB 2002-23893 A	20021014
			WO 2003-GB4446 W	20031014

AB The invention provides an assay for identifying agents which modulate an AGC kinase activity by interacting with a site other than an ATP binding site. Also provided is a phosphorylated and/or unphosphorylated native and/or mutated AGC kinase-derived peptide, polypeptides and/or motifs for use in the assays of the invention, as well as peptides capable of modulating activity of the AGC kinases by interaction through a site other than an ATP binding site.

L7 ANSWER 10 OF 27 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004501625 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15470109
TITLE: Differential roles of PDK1- and PDK2-phosphorylation sites in the yeast AGC kinases Ypk1, Pkc1 and Sch9.
AUTHOR: Roelants Francoise M; Torrance Pamela D; Thorner Jeremy
CORPORATE SOURCE: Department of Molecular and Cell Biology, Division of Biochemistry and Molecular Biology, University of California, Berkeley, CA 94720-3202, USA.
CONTRACT NUMBER: CA09041 (NCI)
GM07232 (NIGMS)
GM21841 (NIGMS)
SOURCE: Microbiology (Reading, England), (2004 Oct) Vol. 150, No. Pt 10, pp. 3289-304.
Journal code: 9430468. ISSN: 1350-0872.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200501
ENTRY DATE: Entered STN: 8 Oct 2004
Last Updated on STN: 14 Jan 2005
Entered Medline: 13 Jan 2005

AB Saccharomyces cerevisiae Pkh1 and Pkh2 (orthologues of mammalian protein kinase, PDK1) are functionally redundant. These kinases activate three AGC family kinases involved in the maintenance of cell wall integrity: Ypk1 and Ypk2, two closely related, functionally redundant enzymes (orthologues of mammalian protein kinase SGK), and Pkc1 (orthologue of mammalian protein kinase PRK2). Pkh1 and Pkh2 activate Ypk1, Ypk2 and Pkc1 by phosphorylating a Thr in a conserved

sequence motif (PDK1 site) within the activation loop of these proteins. A fourth protein kinase involved in growth control and stress response, Sch9 (orthologue of mammalian protein kinase c-Akt/PKB), also carries the conserved activation loop motif. Like other AGC family kinases, Ypk1, Ypk2, Pkc1 and Sch9 also carry a second conserved sequence motif situated in a region C-terminal to the catalytic domain, called the hydrophobic motif (PDK2 site). Currently, there is still controversy surrounding the identity of the enzyme responsible for phosphorylating this second site and the necessity for phosphorylation at this site for in vivo function. Here, genetic and biochemical methods have been used to investigate the physiological consequences of phosphorylation at the PDK1 and PDK2 sites of Ypk1, Pkc1 and Sch9. It was found that phosphorylation at the PDK1 site in the activation loop is indispensable for the essential functions of all three kinases in vivo, whereas phosphorylation at the PDK2 motif plays a non-essential and much more subtle role in modulating the ability of these kinases to regulate the downstream processes in which they participate.

L7 ANSWER 11 OF 27 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2003-12967 BIOTECHDS
TITLE: New crystal of protein kinase B beta, useful for activating protein kinases, e.g. AGC kinases, comprises three-dimensional atomic coordinates or a tetragonal space group;
vector-mediated recombinant protein gene transfer and expression in host cell for use in gene therapy
AUTHOR: BARFORD D; YANG J; HEMMINGS B A; CRON P D
PATENT ASSIGNEE: NOVARTIS FORSCHUNGSSTIFTUNG ZWEIGNIEDERL; CANCER RES INST
PATENT INFO: WO 2003016516 27 Feb 2003
APPLICATION INFO: WO 2002-GB3735 14 Aug 2002
PRIORITY INFO: GB 2002-9985 1 May 2002; GB 2001-19860 14 Aug 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-268328 [26]
AB DERWENT ABSTRACT:
NOVELTY - A crystal of protein kinase Bbeta (PKBbeta) comprising (I), is new.

DETAILED DESCRIPTION - (I) comprises: (a) a tetragonal space group P41212 and unit cell dimensions of: a = 149.33+/-0.5 Angstrom, b = 149.33+/-0.5 Angstrom, c = 39.77+/-0.5 Angstrom; a = 148.40+/-0.5 Angstrom, b = 148.40+/-0.5 Angstrom, c = 38.55+/-0.5 Angstrom; a = 149.70+/-0.5 Angstrom, b = 149.70+/-0.5 Angstrom, c = 39.19+/-0.5 Angstrom; or a = 149.52+/-0.5 Angstrom, b = 149.52+/-0.5 Angstrom, c = 39.06+/-0.5 Angstrom; or (b) the three-dimensional atomic coordinates listed in the specification. INDEPENDENT CLAIMS are also included for: (1) crystallizing (M1) a PKB derivative; (2) determining (M2) the structure of a PKB derivative; (3) a PKB polypeptide having an N-terminus corresponding to Lys-146 of human PKBbeta; (4) a nucleic acid encoding the polypeptide; (5) a vector comprising the nucleic acid; (6) a host cell comprising the nucleic acid or vector; (7) preparing (M3) a polypeptide; (8) analyzing (M4) a PKBbeta-ligand complex; (9) determining (M5) a three-dimensional structure for a target kinase, or for determining three-dimensional atomic coordinate data for a target conformation of a PKB isoform; (10) a computer system or computer-readable media containing: (a) atomic coordinate data listed in the specification, which defines the three-dimensional structure of PKB, or at least its selected coordinates; (b) structure factor data derived from the atomic coordinate data; (c) a Fourier transform of the atomic coordinate data; (d) atomic coordinate data of a target kinase generated by homology modeling of the target based on the data listed in the specification; (e) atomic coordinate data of a target kinase generated by interpreting X-ray crystallographic data or NMR data by reference to any of the data listed in the specification; or (f) structure factor data derived from the atomic coordinate data of (c)-(e); (11) modeling (M6)

the interaction between PKB and an agent compound that modulates PKB activity; (12) identifying (M7) an agent compound that modulates PKB activity; (13) a compound identified as a modulator of PKB activity by M7; (14) inducing (M8) a catalytic domain of an AGC kinase to adopt an active conformation, where the AGC kinase in its native form is regulated by phosphorylation of a regulatory phosphorylation site residue in a C-terminal regulatory segment distinct from the catalytic domain; (15) a non-covalent complex between a catalytic domain of the AGC kinase cited above and an activating agent; (16) determining (M9) the structure of an active conformation of a catalytic domain of the AGC kinase cited above; (17) assessing (M10) the ability of a candidate compound to modulate the catalytic activity of the AGC kinase; and (18) a mutant AGC kinase protein comprising a catalytic domain, a C-terminal regulatory segment distinct from the catalytic domain, and an N-terminus corresponding to residue 139-150 of human PKBbeta, or their corresponding residues in other isoforms, and a mutation which enhances the interaction between the regulatory segment and the catalytic domain relative to the wild-type enzyme, such that an active conformation is induced in the catalytic domain.

BIOTECHNOLOGY - Preferred Crystal: The crystal preferably comprises unit cell dimensions of: a = 149.33 Angstrom, b = 149.33 Angstrom, c = 39.77 Angstrom; a = 148.40 Angstrom, b = 148.40 Angstrom, c = 38.55 Angstrom; a = 149.70 Angstrom, b = 149.70 Angstrom, c = 39.19 Angstrom; or a = 149.52 Angstrom, b = 149.52 Angstrom, c = 39.06 Angstrom. Preferred Polypeptide: The polypeptide comprises a catalytic domain corresponding to residues 146-440 of human PKBbeta. Preferred Method: Crystallizing a PKB derivative comprises producing PKB by recombinant production in a host cell, recovering a PKB derivative from the host, and growing the crystals, where the PKB derivative is a stable protease-resistant form of PKB. The PKB derivative lacks all or substantially all of the PH domain. The derivative has an N-terminus corresponding to Lys-146 of human PKBbeta. The host cell is an insect cell. The method further comprises phosphorylating the PKB derivative in vitro at a residue corresponding to Thr-309 of human PKBbeta. The phosphorylation is performed with PDK1. The crystal is grown by the under oil batch method. Determining the structure of a PKB derivative comprises X-ray diffraction analysis of a crystal produced by the above method. Preparing a polypeptide cited above comprises expressing the polypeptide from the above nucleic acid. Analyzing a PKBbeta-ligand complex comprises employing X-ray crystallographic diffraction data from the PKBbeta-ligand complex, and the three-dimensional structure of PKBbeta to generate a difference Fourier electron density map of the complex, the three-dimensional structure being defined by the atomic coordinate data listed in the specification. Determining a three-dimensional structure for a target kinase comprises aligning a representation of the amino acid sequence of a target kinase of unknown structure with the amino acid sequence of PKBbeta to match homologous regions of the amino acid sequences, modeling the structure of the matched homologous regions of the target kinase on the structure of the corresponding regions of PKBbeta, and determining a conformation for the target kinase which substantially preserves the structure of the matched homologous regions. Alternatively, the method comprises providing the coordinates listed in the specification and positioning the coordinates in the crystal unit cell of the target kinase to provide a structure for the target kinase. The target kinase is an AGC kinase, or its co-complex, derivative or mutant. The AGC kinase is PKBalpha or PKBgamma. Determining three-dimensional atomic coordinate data for a target conformation of a PKB isoform comprises employing the three-dimensional atomic coordinate data listed in the specification or of a template kinase structure, and determining the three-dimensional atomic coordinate data for the target conformation. The template kinase structure is a structure of an AGC kinase or of a murine PKA. Modeling the interaction between PKB and an agent compound that modulates PKB activity comprises employing the three-dimensional atomic coordinate data listed in the specification to

characterize at least one PKBbeta binding site, providing the structure of the agent compound, and fitting the agent compound to the binding site. The agent compound is a peptide comprising the sequence FXXF, YXXF, YXXY, FXXFX (Y/F), YXXFX (Y/F), YXXYX (Y/F), FXXFX', FXXFX' (F/Y), FXX'FX', or FXX'FX' (F/Y); YXXFX', YXXFX' (F/Y), YXX'FX, or YXX'FX' (F/Y); FXXYX', FXXYX' (F/Y), FXX'YX' or FXX'YX' (F/Y); YXXYX', YXXYX' (F/Y), YXX'YX' or YXX'YX' (F/Y), where X' represents an amino acid residue carrying negative charge at physiological pH. In addition, the peptide comprises the sequence FPQFpSY (where pS is phosphoserine), Phe-Pro-Gln-Phe-Asp-Tyr, Phe-Arg-Asp-Phe-Asp-Tyr, Gly-Leu-Leu-Glu-Leu-Asp-Gln-Arg-Thr-His-Phe-Pro-Gln-Phe-Pro-Ser-Tyr-Ser-Ala-Ser-Ile-Arg-Glu, Gly-Leu-Leu-Glu-Leu-Asp-Gln-Arg-Thr-His-Phe-Pro-Gln-Phe-Asp-Tyr-Ser-Ala-Ser-Ile-Arg-Glu or Arg-Glu-Pro-Arg-Ile-Leu-Ser-Glu-Glu-Glu-Gln-Glu-Met-Phe-Arg-Asp-Phe-Asp-Tyr-Ile-Ala-Asp-Trp-Cys. Identifying an agent compound that modulates PKB activity comprises employing the steps of M6 and selecting the candidate compound. A plurality of binding sites are characterized and a plurality of agent compounds are fitted to the sites, and the agent compounds are linked to form a potential modulator compound. The providing step comprises selecting the candidate compound by computationally screening a database of compounds for interaction with the binding site. The method further comprises obtaining or synthesizing the candidate agent compound and contacting the compound with PKB to determine the ability of the compound to interact with PKB. Alternatively, the method further comprise obtaining or synthesizing the candidate agent compound, forming a complex of PKB and the test compound, and analyzing the complex by X-ray crystallography or NMR spectroscopy. The binding site has previously been determined to bind a known agent compound. The known agent compound is a peptide comprising an activation motif that has a hydrophobic motif. The activation motif comprises the peptide sequences cited above. The activation motif further comprises an amino acid residue that carries a negative charge at physiological pH. Inducing a catalytic domain of an AGC kinase to adopt an active conformation comprises providing a polypeptide comprising the catalytic domain and forming a non-covalent complex between the polypeptide and an activating agent, where the contact between the agent and the catalytic domain induces the catalytic domain to adopt an active conformation. The method further comprises phosphorylating the catalytic domain at a position corresponding to residue 309 of human PKBbeta. Determining the structure of an active conformation of a catalytic domain of the AGC kinase cited above, comprises inducing the catalytic domain to adopt an active conformation and obtaining a data set for the conformation, from which a structure may be calculated. The method further comprises crystallizing the catalytic domain in the active conformation, and performing X-ray crystallographic analysis of the crystal. The data set is acquired by NMR. Alternatively, this method comprises providing the above mutant AGC kinase protein and obtaining a data set for the mutant protein from which a structure can be calculated. The regulatory phosphorylation site is substituted with a residue carrying an electrostatic charge at physiological pH. A plurality of contiguous residues of the C-terminal regulatory segment are substituted by the residues from a second AGC kinase, such as PRK2. A mutation is made in the catalytic domain, where the mutation is substitution of at least one of the residues V194I and V198L of human PKBbeta. Assessing the ability of a candidate compound to modulate the catalytic activity of the AGC kinase, comprises providing the polypeptide cited above, forming a non-covalent complex between the polypeptide and an activating agent, and contacting the complex with the candidate agent. The method further comprises measuring the effect of the candidate agent on the AGC kinase activity, and phosphorylating the domain at residue 309 of the PKBbeta.

ACTIVITY - Cytostatic; Antidiabetic; Vasotropic; Nootropic; Neuroprotective. No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The crystal of PKBbeta and methods are useful in activating protein kinases, particularly AGC kinases, for identifying modulators of

protein kinase activity, and for structural analysis of other protein kinases. The crystal may also be used in manufacturing a medicament for treating cancers, diabetes, erectile dysfunction or neurodegeneration.(142 pages)

L7 ANSWER 12 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:991698 HCAPLUS
DOCUMENT NUMBER: 140:37976
TITLE: Crystal structures of human phosphoinositide -dependent protein kinase PDK1 complexes and method for identifying modulators of PDK1 activity
INVENTOR(S): Alessi, Dario; Biondi, Ricardo; Komander, David; Van Aalten, Daan
PATENT ASSIGNEE(S): University of Dundee, UK
SOURCE: PCT Int. Appl., 383 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003104481	A2	20031218	WO 2003-GB2509	20030609
WO 2003104481	A3	20040923		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003241038	A1	20031222	AU 2003-241038	20030609
EP 1513947	A2	20050316	EP 2003-730356	20030609
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.: GB 2002-13186 A 20020608
WO 2003-GB2509 W 20030609

AB A method for selecting or designing a compound for modulating the activity of phosphoinositide dependent protein kinase 1 (PDKI) comprises using mol. modeling means to select or design a compound that is predicted to interact with the protein kinase catalytic domain of PDKI, wherein a 3D structure of at least a part of the protein kinase catalytic domain of PDK1 is compared with a three-dimensional structure of a compound Thus, the crystal structure of residues 51 to 359 of human PDK1 complexed with ATP was determined to 2Å and that of the catalytic domain complexed with staurosporine or with UCN-01 was determined to 2.3 and 2.5Å, resp. A phosphopeptide binding domain consisting of an hydrophobic pocket (PIF binding pocket) defined by residues including Lys115, 20 Ile118, Ile119, Val124, Val127 and/or Leu155 and a phosphate binding pocket defined by residues including Lys76, Arg131, Thr148 and/or Gln150 were identified by anal. of the crystal structure and by mutational anal. UCN-01 was found not to be a specific kinase inhibitor since it inhibited over half of a panel of 29 protein kinases.

L7 ANSWER 13 OF 27 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:317639 SCISEARCH
THE GENUINE ARTICLE: 664UR
TITLE: PKC epsilon is a permissive link in integrin-dependent

IFN-gamma signalling that facilitates JAK phosphorylation of STAT1

AUTHOR: Ivaska J (Reprint); Bosca L; Parker P J

CORPORATE SOURCE: Canc Res UK London Res Inst, Prot Phosphorylat Lab, Lincolns Inn Fields Labs, 44 Lincolns Inn Fields, London WC2A 3PX, England (Reprint); Canc Res UK London Res Inst, Prot Phosphorylat Lab, Lincolns Inn Fields Labs, London WC2A 3PX, England; CSIC, Inst Bioquim, UCM, Fac Farm, E-28040 Madrid, Spain

COUNTRY OF AUTHOR: England; Spain

SOURCE: NATURE CELL BIOLOGY, (APR 2003) Vol. 5, No. 4, pp. 363-369

ISSN: 1465-7392.

PUBLISHER: NATURE PUBLISHING GROUP, MACMILLAN BUILDING, 4 CRINAN ST, LONDON N1 9XW, ENGLAND.

DOCUMENT TYPE: Letter; Journal

LANGUAGE: English

REFERENCE COUNT: 25

ENTRY DATE: Entered STN: 25 Apr 2003
Last Updated on STN: 25 Apr 2003

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The critical dependence of receptor-triggered signals on integrin-mediated cell-substrate. interactions represents a fundamental biological paradigm in health and disease. However, the molecular connections of these permissive inputs, which operate through integrin-matrix interactions, has remained largely obscure. Here we show that the serine-threonine kinase protein kinase C epsilon (PKCepsilon) functions as a signal integrator between cytokine and integrin signalling pathways. Integrins are shown to control PKCepsilon phosphorylation acutely by determining complex formation with protein phosphatase 2A (PP2A) and the upstream kinase PDK1 (phosphoinositide -dependent kinase 1). The PP2A-induced loss of PKCepsilon function results in attenuated interferon gamma (INF-gamma)-induced phosphorylation of STAT1 (signal transducer and activator of transcription 1) downstream of Janus kinase 1/2 (JAK1/2). PKCepsilon function and the IFN-gamma response can be recovered by inhibition of PP2A if PDK1 is associated with PKCepsilon in this complex. More directly, a PP2A-resistant mutant of PKCepsilon is sufficient for restoration of the IFN-gamma response in suspension culture. Thus, PKCepsilon functions as a central point of integration through which integrin engagement exerts a permissive input on IFN-gamma signalling.

L7 ANSWER 14 OF 27 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:204833 BIOSIS

DOCUMENT NUMBER: PREV200400205373

TITLE: The effect of Akt by antidepressants in the rat brain.

AUTHOR(S): Misonoo, A. [Reprint Author]; Kenichi, O. [Reprint Author]; Hsagawa, H. [Reprint Author]; Kiyofumi, T. [Reprint Author]; Kanai, S. [Reprint Author]; Tanaka, D. [Reprint Author]; Hisinuma, T. [Reprint Author]; Fujii, S. [Reprint Author]; Sasuga, Y. [Reprint Author]; Miyamoto, S. [Reprint Author]; Asakura, M. [Reprint Author]

CORPORATE SOURCE: Dept. Neuropsych, St. Marianna Univ. Sch. Med, Kawasaki, Japan

SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 849.15. http://sfn.scholarone.com. e-file.
Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 14 Apr 2004
Last Updated on STN: 14 Apr 2004

AB Akt, also known as protein kinase B, is a protein kinase as a downstream kinase of phosphoinositide 3-kinase (PI3-K) and BDNF. Phoshporylation of residues Ser-473 and Thr-308 is required for Akt activity by PDK1 and PDK2, respectively. PRK2 inhibits the phosphorylation of Akt Ser-473 by PDK1. Key roles for Akt in cellular processes such as apotosis, neurotransmitters release and transcription are now well established.The phosphorylation of Akt Ser-473 and Thr-308 increased after 3 weeks Clomipramine and Fluvoxamine treatment by Immunoblot measurement. PDK1 and PDK1, Ser-241 phosphorylation also increased after treatment of antidepressants. But PI3-K and PRK2 were not changed by antidepressants.Akt is known to play a role in the releasing process for several neurotransmitters (5-HT and NE). It is important cellular mechanism for antidepressants that Akt activated by PDK.

L7 ANSWER 15 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:616256 HCAPLUS
DOCUMENT NUMBER: 137:181594
TITLE: Dominant-negative variants of human protein kinases that inhibit the phosphorylation activity of their active enzyme isoforms
INVENTOR(S): Levine, Zurit; Bernstein, Jeanne
PATENT ASSIGNEE(S): Compugen Ltd., Israel
SOURCE: U.S. Pat. Appl. Publ., 170 pp., Cont.-in-part of U.S. Ser. No. 724,676.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002110811	A1	20020815	US 2001-771161	20010126
US 6936450	B2	20050830		

PRIORITY APPLN. INFO.:
IL 2000-135619 A 20000512
IL 2000-136776 A 20000615
US 2000-724676 A2 20001128

AB The present invention concerns 91 nucleic acid sequences and amino acid sequences of variants of various human kinases, i.e. of sequences which inhibit activity of kinases in a dominant manner. The variants lack a domain or region required for phosphorylation, and thus may be dominant-neg. kinases obtained by alternative splicing of known original sequences of the kinase genes. The novel dominant-neg. kinase variants of the invention are not merely artificially truncated forms, fragments or mutations of known genes, but rather novel sequences which naturally occur within the body of individuals. The invention also concerns pharmaceutical compns. and detection methods using these sequences.
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 16 OF 27 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2002622165 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12177059
TITLE: Regulation of kinase activity of 3-phosphoinositide -dependent protein kinase-1 by binding to 14-3-3.
AUTHOR: Sato Saori; Fujita Naoya; Tsuruo Takashi
CORPORATE SOURCE: Institute of Molecular and Cellular Biosciences, The University of Tokyo, Tokyo 113-0032, Japan.
SOURCE: The Journal of biological chemistry, (2002 Oct 18) Vol. 277, No. 42, pp. 39360-7. Electronic Publication: 2002-08-12.

Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 17 Oct 2002
Last Updated on STN: 5 Jan 2003
Entered Medline: 19 Dec 2002

AB 3-Phosphoinositide-dependent protein kinase-1 (PDK1) plays a central role in activating the protein kinase A, G, and C subfamily. In particular, PDK1 plays an important role in regulating the Akt survival pathway by phosphorylating Akt on Thr-308. PDK1 kinase activity was thought to be constitutively active; however, recent reports suggested that its activity is regulated by binding to other proteins, such as protein kinase C-related kinase-2 (PRK2), p90 ribosomal protein S6 kinase-2 (RSK2), and heat-shock protein 90 (Hsp90). Here we report that PDK1 binds to 14-3-3 proteins in vivo and in vitro through the sequence surrounding Ser-241, a residue that is phosphorylated by itself and is critical for its kinase activity. Mutation of PDK1 to increase its binding to 14-3-3 decreased its kinase activity in vivo. By contrast, mutation of PDK1 to decrease its interaction with 14-3-3 resulted in increased PDK1 kinase activity. Moreover, incubation of wild-type PDK1 with recombinant 14-3-3 in vitro decreased its kinase activity. These data indicate that PDK1 kinase activity is negatively regulated by binding to 14-3-3 through the PDK1 autophosphorylation site Ser-241.

L7 ANSWER 17 OF 27 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:556441 SCISEARCH
THE GENUINE ARTICLE: 565VN
TITLE: Molecular mechanism for the regulation of protein kinase B/Akt by hydrophobic motif phosphorylation
AUTHOR: Yang J; Cron P; Thompson V; Good V M; Hess D; Hemmings B A; Barford D (Reprint)
CORPORATE SOURCE: Friedrich Miescher Inst, Maulbeerstr 66, CH-4048 Basel, Switzerland (Reprint); Friedrich Miescher Inst, CH-4048 Basel, Switzerland; Inst Canc Res, Chester Beatty Labs, Sect Struct Biol, London SW3 6JB, England
COUNTRY OF AUTHOR: Switzerland; England
SOURCE: MOLECULAR CELL, (JUN 2002) Vol. 9, No. 6, pp. 1227-1240. ISSN: 1097-2765.
PUBLISHER: CELL PRESS, 1100 MASSACHUSETTS AVE,, CAMBRIDGE, MA 02138 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 42
ENTRY DATE: Entered STN: 19 Jul 2002
Last Updated on STN: 19 Jul 2002
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Protein kinase B/Akt plays crucial roles in promoting cell survival and mediating insulin responses. The enzyme is stimulated by phosphorylation at two regulatory sites: Thr 309 of the activation segment and Ser 474 of the hydrophobic motif, a conserved feature of many AGC kinases. Analysis of the crystal structures of the unphosphorylated and Thr 309 phosphorylated states of the PKB kinase domain provides a molecular explanation for regulation by Ser 474 phosphorylation. Activation by Ser 474 phosphorylation occurs via a disorder to order transition of the alphaC helix with concomitant restructuring of the activation segment and reconfiguration of the kinase bilobal structure. These conformational changes are mediated by a phosphorylation-promoted interaction of the hydrophobic motif with a channel on the N-terminal lobe induced by the

ordered alphaC helix and are mimicked by peptides corresponding to the hydrophobic motif of PKB and potently by the hydrophobic motif of PRK2.

L7 ANSWER 18 OF 27 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2002055627 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11781095
TITLE: Regulation of both PDK1 and the phosphorylation of PKC-zeta and -delta by a C-terminal PRK2 fragment.
AUTHOR: Hodgkinson Conrad P; Sale Graham J
CORPORATE SOURCE: Division of Biochemistry and Molecular Biology, School of Biological Sciences, University of Southampton, Southampton, UK.
SOURCE: Biochemistry, (2002 Jan 15) Vol. 41, No. 2, pp. 561-9. Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 25 Jan 2002
Last Updated on STN: 20 Apr 2002
Entered Medline: 4 Feb 2002

AB The mechanism by which PDK1 regulates AGC kinases remains unclear. To further understand this process, we performed a yeast two-hybrid screen using PDK1 as bait. PKC-zeta, PKC-delta, and PRK2 were identified as interactors of PDK1. A combination of yeast two-hybrid binding assays and coprecipitation from mammalian cells was used to characterize the nature of the PDK1 -PKC interaction. The presence of the PH domain of PDK1 inhibited the interaction of PDK1 with the PKCs. A contact region of PDK1 was mapped between residues 314 and 408. The interaction of PDK1 with the PKCs required the full-length PKC-zeta and -delta proteins apart from their C-terminal tails. PDK1 was able to phosphorylate full-length PKC-zeta and -delta but not PKC-zeta and -delta constructs containing the PDK1 phosphorylation site but lacking the C-terminal tails. A C-terminal PRK2 fragment, normally produced by caspase-3 cleavage during apoptosis, inhibited PDK1 autophosphorylation by >90%. The ability of PDK1 to phosphorylate PKC-zeta and -delta in vitro was also markedly inhibited by the PRK2 fragment. Additionally, generation of the PRK2 fragment in vivo inhibited by >90% the phosphorylation of endogenous PKC-zeta by PDK1. In conclusion, these results show that the C-terminal tail of PKC is a critical determinant for PKC-zeta and -delta phosphorylation by PDK1. Moreover, the C-terminal PRK2 fragment acts as a potent negative regulator of PDK1 autophosphorylation and PDK1 kinase activity against PKC-zeta and -delta. As the C-terminal PRK2 fragment is naturally generated during apoptosis, this may provide a mechanism of restraining prosurvival signals during apoptosis.

L7 ANSWER 19 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:453281 HCAPLUS
DOCUMENT NUMBER: 135:73331
TITLE: Method for identifying modulators of protein kinases PDK1, SGK, S6 kinase, PRK2, and protein kinases A, B, and C
INVENTOR(S): Alessi, Dario; Biondi, Ricardo
PATENT ASSIGNEE(S): University of Dundee, UK
SOURCE: PCT Int. Appl., 180 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001044497	A2	20010621	WO 2000-GB4598	20001204
WO 2001044497	A3	20020314		
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1234188	A2	20020828	EP 2000-985454	20001204
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
JP 2003516760	T2	20030520	JP 2001-545574	20001204
US 2003143656	A1	20030731	US 2003-148786	20030108
PRIORITY APPLN. INFO.:			US 1999-168559P P	19991202
			WO 2000-GB4598 W	20001204

AB A method of identifying a compound that modulates the protein kinase activity of a protein kinase having a hydrophobic pocket in the position equivalent to the hydrophobic pocket of Protein Kinase A (PKA) that is defined by residues including Lys76, Leu116, Val80 and/or Lys111 of full-length mouse PKA, wherein the ability of the compound to inhibit, promote or mimic the interaction of the said hydrophobic pocket-containing protein kinase with an interacting polypeptide is measured and a compound that inhibits, promotes or mimics the said interaction is selected, wherein the interacting polypeptide interacts with the hydrophobic pocket of the protein kinase and/or comprises the amino acid sequence Phe/Tyr-Xaa-Xaa-Phe/Tyr. The protein kinase may be PDK1, PKB, SGK or p70 S6 kinase. A method of identifying a compound that modulates the protein kinase activity of a protein kinase having a hydrophobic pocket as defined above, for example PDK1, comprising the steps of (1) determining the effect of a test compound on the protein kinase activity of the said protein kinase, and/or a mutant thereof, and (2) selecting a compound capable of modulating the protein kinase activity of the said protein kinase to different extents towards (i) a substrate that binds to the said hydrophobic pocket of the said protein kinase (hydrophobic pocket-dependent substrate) and (ii) a substrate (such as PKB) that does not bind, or binds to a lesser extent than the first said substrate (hydrophobic pocket-independent substrate), to the said hydrophobic pocket of the said protein kinase. The protein kinase modulators identified may be used in treatment of cancer and diabetes.

L7 ANSWER 20 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:688348 HCAPLUS
DOCUMENT NUMBER: 133:278041
TITLE: Altered specificity of phosphoinositide -dependent protein kinase PDK1 in presence of substrate consensus peptides
INVENTOR(S): Alessi, Dario; Balendran, Anudharan; Deak, Maria; Currie, Richard; Downes, Peter; Casamayor, Antonio
PATENT ASSIGNEE(S): University of Dundee, UK
SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000056864	A2	20000928	WO 2000-GB1004	20000317
WO 2000056864	A3	20010118		
W: JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,				

PT, SE
EP 1165761 A2 20020102 EP 2000-911069 20000317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
JP 2002539780 T2 20021126 JP 2000-606723 20000317
PRIORITY APPLN. INFO.: GB 1999-6245 A 19990319
WO 2000-GB1004 W 20000317

OTHER SOURCE(S): MARPAT 133:278041

AB A method of altering the substrate specificity of phosphoinositide -dependent protein kinase 1 (PDK1) is provided, wherein the said PDK1 is exposed to a polypeptide which comprises the amino acid sequence Phe/Tyr-Xaa-Xaa-Phe/Tyr-Zaa-Phe/Tyr wherein Zaa represents a neg. charged amino acid residue. The PDK1 with altered substrate specificity is capable of phosphorylating the Ser/Thr residue in a polypeptide with an amino acid sequence corresponding to the consensus sequence Phe/Tyr-Xaa-Xaa-Phe/Tyr-Ser/Thr-Phe/Tyr. The PDK1 with altered specificity may be useful in screening assays and for phosphorylating substrates having the above consensus sequence.

L7 ANSWER 21 OF 27 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2001098534 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11006271
TITLE: Mechanism of phosphorylation of protein kinase B/Akt by a constitutively active 3-phosphoinositide -dependent protein kinase-1.
AUTHOR: Wick M J; Dong L Q; Riojas R A; Ramos F J; Liu F
CORPORATE SOURCE: Departments of Pharmacology and Biochemistry, The University of Texas Health Science Center, San Antonio, Texas 78229, USA.
CONTRACT NUMBER: DK56166 (NIDDK)
SOURCE: The Journal of biological chemistry, (2000 Dec 22) Vol. 275, No. 51, pp. 40400-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 20 Apr 2002
Entered Medline: 1 Feb 2001

AB Phosphorylation of Thr(308) in the activation loop and Ser(473) at the carboxyl terminus is essential for protein kinase B (PKB/Akt) activation. However, the biochemical mechanism of the phosphorylation remains to be characterized. Here we show that expression of a constitutively active mutant of mouse 3-phosphoinositide-dependent protein kinase-1 (PDK1(A280V)) in Chinese hamster ovary cells overexpressing the insulin receptor was sufficient to induce PKB phosphorylation at Thr(308) to approximately the same extent as insulin stimulation. Phosphorylation of PKB by PDK1(A280V) was not affected by treatment of cells with inhibitors of phosphatidylinositol 3-kinase or by deletion of the pleckstrin homology (PH) domain of PKB. C(2)-ceramide, a cell-permeable, indirect inhibitor of PKB phosphorylation, did not inhibit PDK1(A280V)-catalyzed PKB phosphorylation in cells and had no effect on PDK1 activity in vitro. On the other hand, co-expression of full-length protein kinase C-related kinase-1 (PRK1/PKN) or 2 (PRK2) inhibited PDK1 (A280V)-mediated PKB phosphorylation. Replacing alanine at position 280 with valine or deletion of the PH domain enhanced PDK1 autophosphorylation in vitro. However, deletion of the PH domain of PDK1(A280V) significantly reduced PDK1(A280V)-mediated phosphorylation of PKB in cells. In resting cells, PDK1(A280V) localized in the cytosol and at the plasma membrane. However,

PDK1(A280V) lacking the PH domain localized predominantly in the cytosol. Taken together, our findings suggest that the wild-type PDK1 may not be constitutively active in cells. In addition, activation of PDK1 is sufficient to phosphorylate PKB at Thr(308) in the cytosol. Furthermore, the PH domain of PDK1 may play both positive and negative roles in regulating the in vivo function of the enzyme. Finally, unlike the carboxyl-terminal fragment of PRK2, which has been shown to bind PDK1 and allow the enzyme to phosphorylate PKB at both Thr(308) and Ser(473), full-length PRK2 and its related kinase PRK1/PKN may both play negative roles in PKB-mediated downstream biological events.

L7 ANSWER 22 OF 27 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2000396616 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10764742
TITLE: A 3-phosphoinositide-dependent protein kinase-1 (PDK1) docking site is required for the phosphorylation of protein kinase Czeta (PKCzeta) and PKC-related kinase 2 by PDK1.
AUTHOR: Balendran A; Biondi R M; Cheung P C; Casamayor A; Deak M; Alessi D R
CORPORATE SOURCE: MRC Protein Phosphorylation Unit, Division of Signal Transduction Therapy, MSI/WTB Complex, University of Dundee, Dow Street, Dundee DD1 5EH, Scotland, United Kingdom.
SOURCE: The Journal of biological chemistry, (2000 Jul 7) Vol. 275, No. 27, pp. 20806-13.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 24 Aug 2000
Last Updated on STN: 20 Apr 2002
Entered Medline: 16 Aug 2000

AB Members of the AGC subfamily of protein kinases including protein kinase B, p70 S6 kinase, and protein kinase C (PKC) isoforms are activated and/or stabilized by phosphorylation of two residues, one that resides in the T-loop of the kinase domain and the other that is located C-terminal to the kinase domain in a region known as the hydrophobic motif. Atypical PKC isoforms, such as PKCzeta, and the PKC-related kinases, like PRK2, are also activated by phosphorylation of their T-loop site but, instead of possessing a phosphorylatable Ser/Thr in their hydrophobic motif, contain an acidic residue. The 3-phosphoinositide -dependent protein kinase (PDK1) activates many members of the AGC subfamily of kinases in vitro, including PKCzeta and PRK2 by phosphorylating the T-loop residue. In the present study we demonstrate that the hydrophobic motifs of PKCzeta and PKCiota, as well as PRK1 and PRK2, interact with the kinase domain of PDK1. Mutation of the conserved residues of the hydrophobic motif of full-length PKCzeta, full-length PRK2, or PRK2 lacking its N-terminal regulatory domain abolishes or significantly reduces the ability of these kinases to interact with PDK1 and to become phosphorylated at their T-loop sites in vivo. Furthermore, overexpression of the hydrophobic motif of PRK2 in cells prevents the T-loop phosphorylation and thus inhibits the activation of PRK2 and PKCzeta. These findings indicate that the hydrophobic motif of PRK2 and PKCzeta acts as a "docking site" enabling the recruitment of PDK1 to these substrates. This is essential for their phosphorylation by PDK1 in cells.

L7 ANSWER 23 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:270248 HCAPLUS

DOCUMENT NUMBER: 133:70575
TITLE: Rho GTPase control of protein kinase C-related protein kinase activation by 3-phosphoinositide -dependent protein kinase
AUTHOR(S): Flynn, Peter; Mellor, Harry; Casamassima, Adele; Parker, Peter J.
CORPORATE SOURCE: Imperial Cancer Research Fund, Protein Phosphorylation Laboratory, London, WC2A 3PX, UK
SOURCE: Journal of Biological Chemistry (2000), 275(15), 11064-11070
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The protein kinase C-related protein kinases (PRKs) have been shown to be under the control of the Rho GTPases and influenced by autophosphorylation. In analyzing the relationship between these inputs, it is shown that activation in vitro and in vivo involves the activation loop phosphorylation of PRK1/2 by 3-phosphoinositide-dependent protein kinase-1 (PDK1). Rho overexpression in cultured cells is shown to increase the activation loop phosphorylation of endogenous PRKs and is demonstrated to influence this process by controlling the ability of PRKs to bind to PDK1. The interaction of PRK1/2 with PDK1 is shown to be dependent upon Rho. Direct demonstration of ternary (Rho·PRK·PDK1) complex formation in situ is provided by the observation that PDK1 is recruited to RhoB-containing endosomes only if PRK is coexpressed. Furthermore, this in vivo complex is maintained after phosphoinositide 3-kinase inhibition. The control of PRKs by PDK1 thus evidences a novel strategy of substrate-directed control involving GTPases.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 24 OF 27 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2000164465 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10698939
TITLE: Identification of a pocket in the PDK1 kinase domain that interacts with PIF and the C-terminal residues of PKA.
AUTHOR: Biondi R M; Cheung P C; Casamayor A; Deak M; Currie R A; Alessi D R
CORPORATE SOURCE: Divison of Signal Transduction Therapy, MSI/WTB Complex, University of Dundee, Dow Street, Dundee DD1 5EH, UK.. rbiondi@bad.dundee.ac.uk
SOURCE: The EMBO journal, (2000 Mar 1) Vol. 19, No. 5, pp. 979-88. Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 5 May 2000
Last Updated on STN: 20 Apr 2002
Entered Medline: 26 Apr 2000

AB The 3-phosphoinositide-dependent protein kinase-1 (PDK1) phosphorylates and activates a number of protein kinases of the AGC subfamily. The kinase domain of PDK1 interacts with a region of protein kinase C-related kinase-2 (PRK2), termed the PDK1-interacting fragment (PIF), through a hydrophobic motif. Here we identify a hydrophobic pocket in the small lobe of the PDK1 kinase domain, separate from the ATP- and substrate-binding sites, that interacts with PIF. Mutation of residues predicted to form

part of this hydrophobic pocket either abolished or significantly diminished the affinity of PDK1 for PIF. PIF increased the rate at which PDK1 phosphorylated a synthetic dodecapeptide (T308tide), corresponding to the sequences surrounding the PDK1 phosphorylation site of PKB. This peptide is a poor substrate for PDK1, but a peptide comprising T308tide fused to the PDK1 -binding motif of PIF was a vastly superior substrate for PDK1. Our results suggest that the PIF-binding pocket on the kinase domain of PDK1 acts as a 'docking site', enabling it to interact with and enhance the phosphorylation of its substrates.

L7 ANSWER 25 OF 27 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2001061082 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11078882
TITLE: Further evidence that 3-phosphoinositide -dependent protein kinase-1 (PDK1) is required for the stability and phosphorylation of protein kinase C (PKC) isoforms.
AUTHOR: Balendran A; Hare G R; Kieloch A; Williams M R; Alessi D R
CORPORATE SOURCE: MRC Protein Phosphorylation, MSI/WTB complex, University of Dundee, Dow Street, DD1 5EH, Dundee, UK.
SOURCE: FEBS letters, (2000 Nov 10) Vol. 484, No. 3, pp. 217-23. Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 20 Apr 2002
Entered Medline: 22 Dec 2000

AB The multi-site phosphorylation of the protein kinase C (PKC) superfamily plays an important role in the regulation of these enzymes. One of the key phosphorylation sites required for the activation of all PKC isoforms lies in the T-loop of the kinase domain. Recent in vitro and transfection experiments indicate that phosphorylation of this residue can be mediated by the 3-phosphoinositide-dependent protein kinase-1 (PDK1). In this study, we demonstrate that in embryonic stem (ES) cells lacking PDK1 (PDK1-/- cells), the intracellular levels of endogenously expressed PKCalpha, PKCbetaI, PKCgamma, PKCdelta, PKCepsilon, and PKC-related kinase-1 (PRK1) are vastly reduced compared to control ES cells (PDK1+/+ cells). The levels of PKCzeta and PRK2 protein are only moderately reduced in the PDK1-/- ES cells. We demonstrate that in contrast to PKCzeta expressed PDK1+/+ ES cells, PKCzeta in ES cells lacking PDK1 is not phosphorylated at its T-loop residue. This provides the first genetic evidence that PKCzeta is a physiological substrate for PDK1. In contrast, PRK2 is still partially phosphorylated at its T-loop in PDK1-/- cells, indicating the existence of a PDK1 -independent mechanism for the phosphorylation of PRK2 at this residue.

L7 ANSWER 26 OF 27 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:386006 BIOSIS
DOCUMENT NUMBER: PREV199900386006
TITLE: Kinase phosphorylation: Keeping it all in the family.
AUTHOR(S): Peterson, Randall T. [Reprint author]; Schreiber, Stuart L. [Reprint author]
CORPORATE SOURCE: Departments of Chemistry and Chemical Biology and Molecular and Cellular Biology, Howard Hughes Medical Institute, Harvard University, Cambridge, MA, 02138, USA
SOURCE: Current Biology, (July 15, 1999) Vol. 9, No. 14, pp. R521-R524. print.

CODEN: CUBLE2. ISSN: 0960-9822.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Sep 1999
Last Updated on STN: 28 Sep 1999

AB The identification of PDK1 as a kinase that phosphorylates the AGC family of kinases led to a hunt for 'PDK2', a hypothetical regulated kinase(s) that would be required for full activation of the AGC kinases. Recent findings suggest that the elusive PDK2 may actually be a familiar kinase with an atypical associate.

L7 ANSWER 27 OF 27 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 1999244939 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10226025
TITLE: PDK1 acquires PDK2 activity in the presence of a synthetic peptide derived from the carboxyl terminus of PRK2.
AUTHOR: Balendran A; Casamayor A; Deak M; Paterson A; Gaffney P; Currie R; Downes C P; Alessi D R
CORPORATE SOURCE: MRC Protein Phosphorylation Unit, Department of Biochemistry, University of Dundee, Dundee DD1 5EH, UK.
SOURCE: Current biology : CB, (1999 Apr 22) Vol. 9, No. 8, pp. 393-404.
Journal code: 9107782. ISSN: 0960-9822.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 14 Jun 1999
Last Updated on STN: 20 Apr 2002
Entered Medline: 1 Jun 1999

AB BACKGROUND: Protein kinase B (PKB) is activated by phosphorylation of Thr308 and of Ser473. Thr308 is phosphorylated by the 3-phosphoinositide-dependent protein kinase-1 (PDK1) but the identity of the kinase that phosphorylates Ser473 (provisionally termed PDK2) is unknown. RESULTS: The kinase domain of PDK1 interacts with a region of protein kinase C-related kinase-2 (PRK2), termed the PDK1-interacting fragment (PIF). PIF is situated carboxy-terminal to the kinase domain of PRK2, and contains a consensus motif for phosphorylation by PDK2 similar to that found in PKBalpha, except that the residue equivalent to Ser473 is aspartic acid. Mutation of any of the conserved residues in the PDK2 motif of PIF prevented interaction of PIF with PDK1. Remarkably, interaction of PDK1 with PIF, or with a synthetic peptide encompassing the PDK2 consensus sequence of PIF, converted PDK1 from an enzyme that could phosphorylate only Thr308 of PKBalpha to one that phosphorylates both Thr308 and Ser473 of PKBalpha in a manner dependent on phosphatidylinositol (3,4,5) trisphosphate (PtdIns(3,4,5)P3). Furthermore, the interaction of PIF with PDK1 converted the PDK1 from a form that is not directly activated by PtdIns(3,4,5)P3 to a form that is activated threefold by PtdIns(3,4,5)P3. We have partially purified a kinase from brain extract that phosphorylates Ser473 of PKBalpha in a PtdIns(3,4,5)P3-dependent manner and that is immunoprecipitated with PDK1 antibodies. CONCLUSIONS: PDK1 and PDK2 might be the same enzyme, the substrate specificity and activity of PDK1 being regulated through its interaction with another protein(s). PRK2 is a probable substrate for PDK1.

=> d his

(FILE 'HOME' ENTERED AT 10:08:25 ON 28 JUL 2006)

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     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 10:08:53 ON 28 JUL 2006
L1         67106 S PHOSPHOINOSITIDE
L2         19704 S L1 (2W) KINASE##
L3          2205 S PDK1
L4         20665 S L2 OR L3
L5           319 S PRK2
L6            60 S L4 AND L5
L7            27 DUP REM L6 (33 DUPLICATES REMOVED)

=> s l5 and pif
L8            12 L5 AND PIF

=> dup rem l18
L18 IS NOT VALID HERE
The L-number entered has not been defined in this session, or it
has been deleted.  To see the L-numbers currently defined in this
session, enter DISPLAY HISTORY at an arrow prompt (=>).

=> dup rem l8
PROCESSING COMPLETED FOR L8
L9             3 DUP REM L8 (9 DUPLICATES REMOVED)

=> d 1-3 ibib ab

L9   ANSWER 1 OF 3  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2003:991698  HCAPLUS
DOCUMENT NUMBER:          140:37976
TITLE:                    Crystal structures of human phosphoinositide-dependent
                          protein kinase PDK1 complexes and method for
                          identifying modulators of PDK1 activity
INVENTOR(S):              Alessi, Dario; Biondi, Ricardo; Komander, David; Van
                          Aalten, Daan
PATENT ASSIGNEE(S):       University of Dundee, UK
SOURCE:                   PCT Int. Appl., 383 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
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     WO 2003104481         A2    20031218    WO 2003-GB2509          20030609
     WO 2003104481         A3    20040923
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
             PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
             TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     AU 2003241038         A1    20031222    AU 2003-241038          20030609
     EP 1513947            A2    20050316    EP 2003-730356          20030609
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
PRIORITY APPLN. INFO.:                       GB 2002-13186       A  20020608
                                             WO 2003-GB2509      W  20030609
AB   A method for selecting or designing a compound for modulating the activity
     of phosphoinositide dependent protein kinase 1 (PDKI) comprises using mol.
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modeling means to select or design a compound that is predicted to interact with the protein kinase catalytic domain of PDKI, wherein a 3D structure of at least a part of the protein kinase catalytic domain of PDK1 is compared with a three-dimensional structure of a compound Thus, the crystal structure of residues 51 to 359 of human PDK1 complexed with ATP was determined to 2Å and that of the catalytic domain complexed with staurosporine or with UCN-01 was determined to 2.3 and 2.5Å, resp. A phosphopeptide binding domain consisting of an hydrophobic pocket (PIF binding pocket) defined by residues including Lys115, 20 Ile118, Ile119, Val124, Val127 and/or Leu155 and a phosphate binding pocket defined by residues including Lys76, Arg131, Thr148 and/or Gln150 were identified by anal. of the crystal structure and by mutational anal. UCN-01 was found not to be a specific kinase inhibitor since it inhibited over half of a panel of 29 protein kinases.

L9 ANSWER 2 OF 3 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2000164465 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10698939
TITLE: Identification of a pocket in the PDK1 kinase domain that interacts with PIF and the C-terminal residues of PKA.
AUTHOR: Biondi R M; Cheung P C; Casamayor A; Deak M; Currie R A; Alessi D R
CORPORATE SOURCE: Divison of Signal Transduction Therapy, MSI/WTB Complex, University of Dundee, Dow Street, Dundee DD1 5EH, UK.. rbiondi@bad.dundee.ac.uk
SOURCE: The EMBO journal, (2000 Mar 1) Vol. 19, No. 5, pp. 979-88. Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 5 May 2000
Last Updated on STN: 20 Apr 2002
Entered Medline: 26 Apr 2000
AB The 3-phosphoinositide-dependent protein kinase-1 (PDK1) phosphorylates and activates a number of protein kinases of the AGC subfamily. The kinase domain of PDK1 interacts with a region of protein kinase C-related kinase-2 (PRK2), termed the PDK1-interacting fragment (PIF), through a hydrophobic motif. Here we identify a hydrophobic pocket in the small lobe of the PDK1 kinase domain, separate from the ATP- and substrate-binding sites, that interacts with PIF. Mutation of residues predicted to form part of this hydrophobic pocket either abolished or significantly diminished the affinity of PDK1 for PIF . PIF increased the rate at which PDK1 phosphorylated a synthetic dodecapeptide (T308tide), corresponding to the sequences surrounding the PDK1 phosphorylation site of PKB. This peptide is a poor substrate for PDK1, but a peptide comprising T308tide fused to the PDK1-binding motif of PIF was a vastly superior substrate for PDK1. Our results suggest that the PIF-binding pocket on the kinase domain of PDK1 acts as a 'docking site', enabling it to interact with and enhance the phosphorylation of its substrates.

L9 ANSWER 3 OF 3 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 1999244939 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10226025
TITLE: PDK1 acquires PDK2 activity in the presence of a synthetic peptide derived from the carboxyl terminus of PRK2 .
AUTHOR: Balendran A; Casamayor A; Deak M; Paterson A; Gaffney P; Currie R; Downes C P; Alessi D R
CORPORATE SOURCE: MRC Protein Phosphorylation Unit, Department of Biochemistry, University of Dundee, Dundee DD1 5EH, UK.

SOURCE: Current biology : CB, (1999 Apr 22) Vol. 9, No. 8, pp. 393-404.
Journal code: 9107782. ISSN: 0960-9822.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 14 Jun 1999
Last Updated on STN: 20 Apr 2002
Entered Medline: 1 Jun 1999

AB BACKGROUND: Protein kinase B (PKB) is activated by phosphorylation of Thr308 and of Ser473. Thr308 is phosphorylated by the 3-phosphoinositide-dependent protein kinase-1 (PDK1) but the identity of the kinase that phosphorylates Ser473 (provisionally termed PDK2) is unknown. RESULTS: The kinase domain of PDK1 interacts with a region of protein kinase C-related kinase-2 (PRK2), termed the PDK1-interacting fragment (PIF). PIF is situated carboxy-terminal to the kinase domain of PRK2, and contains a consensus motif for phosphorylation by PDK2 similar to that found in PKBalpha, except that the residue equivalent to Ser473 is aspartic acid. Mutation of any of the conserved residues in the PDK2 motif of PIF prevented interaction of PIF with PDK1. Remarkably, interaction of PDK1 with PIF, or with a synthetic peptide encompassing the PDK2 consensus sequence of PIF, converted PDK1 from an enzyme that could phosphorylate only Thr308 of PKBalpha to one that phosphorylates both Thr308 and Ser473 of PKBalpha in a manner dependent on phosphatidylinositol (3,4,5) trisphosphate (PtdIns(3,4,5)P3). Furthermore, the interaction of PIF with PDK1 converted the PDK1 from a form that is not directly activated by PtdIns(3,4,5)P3 to a form that is activated threefold by PtdIns(3,4,5)P3. We have partially purified a kinase from brain extract that phosphorylates Ser473 of PKBalpha in a PtdIns(3,4,5)P3-dependent manner and that is immunoprecipitated with PDK1 antibodies. CONCLUSIONS: PDK1 and PDK2 might be the same enzyme, the substrate specificity and activity of PDK1 being regulated through its interaction with another protein(s). PRK2 is a probable substrate for PDK1.

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=> d his

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L1         67106 S PHOSPHOINOSITIDE
L2         19704 S L1 (2W) KINASE##
L3          2205 S PDK1
L4         20665 S L2 OR L3
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L7            27 DUP REM L6 (33 DUPLICATES REMOVED)
L8            12 S L5 AND PIF
L9             3 DUP REM L8 (9 DUPLICATES REMOVED)

=> s pkc (w)related
L10          346 PKC (W) RELATED

=> s l5 and l10
L11           43 L5 AND L10

=> dup rem l11
PROCESSING COMPLETED FOR L11
L12           31 DUP REM L11 (12 DUPLICATES REMOVED)
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L12 ANSWER 1 OF 31 MEDLINE on STN
ACCESSION NUMBER: 2006151396 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16441511
TITLE: Neuronal responses to myelin are mediated by rho kinase.
AUTHOR: Alabed Yazan Z; Grados-Munro Edith; Ferraro Gino B; Hsieh Sidney H-K; Fournier Alyson E
CORPORATE SOURCE: Department of Neurology and Neurosurgery, Montreal Neurological Institute, Montreal, Quebec, Canada.
SOURCE: Journal of neurochemistry, (2006 Mar) Vol. 96, No. 6, pp. 1616-25. Electronic Publication: 2006-01-25.
Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200605
ENTRY DATE: Entered STN: 17 Mar 2006
Last Updated on STN: 11 May 2006
Entered Medline: 10 May 2006

AB CNS myelin inhibits axon growth due to the expression of several growth-inhibitory proteins, including myelin-associated glycoprotein, oligodendrocyte myelin glycoprotein and Nogo. Myelin-associated inhibitory proteins activate rho GTPase in responsive neurons. Rho kinase (ROCK) has been implicated as a critical rho effector in this pathway due to the ability of the pharmacological inhibitor Y-27632 to circumvent myelin-dependent inhibition. Y-27632, however, inhibits the activity of additional kinases. Using three independent approaches, we provide direct evidence that ROCKII is activated in response to the myelin-associated inhibitor Nogo. We demonstrate that Nogo treatment enhances ROCKII translocation to the cellular membrane in PC12 cells and enhances ROCKII kinase activity towards an in vitro substrate. In addition, Nogo treatment enhances phosphorylation of myosin light chain II, a known ROCK substrate. Further, we demonstrate that primary dorsal root ganglia neurons can be rendered insensitive to the inhibitory effects of myelin via infection with dominant negative ROCK. Together these data provide direct evidence for a rho-ROCK-myosin light chain-II signaling cascade in response to myelin-associated inhibitors.

L12 ANSWER 2 OF 31 MEDLINE on STN
ACCESSION NUMBER: 2004584710 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15364941
TITLE: Protein kinase C-related kinase 2 regulates hepatitis C virus RNA polymerase function by phosphorylation.
AUTHOR: Kim Seong-Jun; Kim Jung-Hee; Kim Yeon-Gu; Lim Ho-Soo; Oh Jong-Won
CORPORATE SOURCE: Department of Biotechnology, Yonsei University, Seoul 120-749, Korea.
SOURCE: The Journal of biological chemistry, (2004 Nov 26) Vol. 279, No. 48, pp. 50031-41. Electronic Publication: 2004-09-13.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200502
ENTRY DATE: Entered STN: 24 Nov 2004
Last Updated on STN: 8 Feb 2005
Entered Medline: 7 Feb 2005

AB The hepatitis C virus (HCV) NS5B protein is the viral RNA-dependent RNA polymerase required for replication of the HCV RNA genome. We have

identified a peptide that most closely resembles a short region of the protein kinase C-related kinase 2 (PRK2) by screening of a random 12-mer peptide library displayed on the surface of the M13 bacteriophage with NS5B proteins immobilized on microwell plates. Competitive phage enzyme-linked immunosorbent assay with a synthetic peptide showed that the phage clone displaying this peptide could bind HCV RNA polymerase with a high affinity. Coimmunoprecipitation and colocalization studies demonstrated in vivo interaction of NS5B with PRK2. In vitro kinase assays demonstrated that PRK2 specifically phosphorylates NS5B by interaction with the N-terminal finger domain of NS5B (amino acids 1-187). Consistent with the in vitro NS5B-phosphorylating activity of PRK2, we detected the phosphorylated form of NS5B by metabolic cell labeling. Furthermore, HCV NS5B immunoprecipitated from HCV subgenomic replicon cells was specifically recognized by an antiphosphoserine antibody. Knock-down of the endogenous PRK2 expression using a PRK2-specific small interfering RNA inhibited HCV RNA replication. In contrast, PRK2 overexpression, which was accompanied by an increase of in the level of its active form, dramatically enhanced HCV RNA replication. Altogether, our results indicate that HCV RNA replication is regulated by NS5B phosphorylation by PRK2.

L12 ANSWER 3 OF 31 MEDLINE on STN
ACCESSION NUMBER: 2003239781 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12626518
TITLE: The yersinia virulence factor YopM forms a novel protein complex with two cellular kinases.
AUTHOR: McDonald Christine; Vacratsis Panayiotis O; Bliska James B; Dixon Jack E
CORPORATE SOURCE: Department of Biological Chemistry, University of Michigan Medical School, Life Sciences Institute, Ann Arbor, Michigan 48109, USA.
CONTRACT NUMBER: R01 AI43389 (NIAID)
R01 DK18849 (NIDDK)
R37 DK18024 (NIDDK)
SOURCE: The Journal of biological chemistry, (2003 May 16) Vol. 278, No. 20, pp. 18514-23. Electronic Publication: 2003-03-06.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 24 May 2003
Last Updated on STN: 26 Jun 2003
Entered Medline: 25 Jun 2003

AB Pathogenic Yersinia contain a virulence plasmid that encodes genes for intracellular effectors, which neutralize the host immune response. One effector, YopM, is necessary for Yersinia virulence, but its function in host cells is unknown. To identify potential cellular pathways affected by YopM, proteins that co-immunoprecipitate with YopM in mammalian cells were isolated and identified by mass spectrometry. Results demonstrate that two kinases, protein kinase C-like 2 (PRK2) and ribosomal S6 protein kinase 1 (RSK1), interact directly with YopM. These two kinases associate only when YopM is present, and expression of YopM in cells stimulates the activity of both kinases. RSK1 is activated directly by interaction with YopM, and RSK1 kinase activity is required for YopM-stimulated PRK2 activity. YopM activation of RSK1 occurs independently of the actions of YopJ on the MAPK pathway. YopM is also required for Yersinia-induced changes in RSK1 mobility in infected macrophage cells. These results identify the first intracellular targets of YopM and suggest YopM acts to stimulate the activity of PRK2 and RSK1.

L12 ANSWER 4 OF 31 MEDLINE on STN
ACCESSION NUMBER: 2003279476 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12748390
TITLE: The receptor kinases LePRK1 and LePRK2 associate in pollen and when expressed in yeast, but dissociate in the presence of style extract.
AUTHOR: Wengier Diego; Valsecchi Isabel; Cabanas Maria Laura; Tang Wei-hua; McCormick Sheila; Muschietti Jorge
CORPORATE SOURCE: Instituto de Ingenieria Genetica y Biologia Molecular, Consejo Nacional de Investigaciones Cientificas y Tecnicas de Argentina, Departamento de Fisiologia y Biologia Molecular y Celular-Universidad de Buenos Aires, Obligado 2490, Argentina.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2003 May 27) Vol. 100, No. 11, pp. 6860-5. Electronic Publication: 2003-05-14. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 17 Jun 2003
Last Updated on STN: 17 Jul 2003
Entered Medline: 16 Jul 2003

AB After pollen grains germinate on the stigma, pollen tubes traverse the extracellular matrix of the style on their way to the ovules. We previously characterized two pollen-specific, receptor-like kinases, LePRK1 and LePRK2, from tomato (Lycopersicon esculentum). Their structure and immunolocalization pattern and the specific dephosphorylation of LePRK2 suggested that these kinases might interact with signaling molecules in the style extracellular matrix. Here, we show that LePRK1 and LePRK2 can be coimmunoprecipitated from pollen or when expressed together in yeast. In yeast, their association requires LePRK2 kinase activity. In pollen, LePRK1 and LePRK2 are found in an approximately 400-kDa protein complex that persists on pollen germination, but this complex is disrupted when pollen is germinated in vitro in the presence of style extract. In yeast, the addition of style extract also disrupts the interaction between LePRK1 and LePRK2. Fractionation of the style extract reveals that the disruption activity is enriched in the 3- to 10-kDa fraction. A component(s) in this fraction also is responsible for the specific dephosphorylation of LePRK2. The style component(s) that dephosphorylates LePRK2 is likely to be a heat-stable peptide that is present in exudate from the style. The generally accepted model of receptor kinase signaling involves binding of a ligand to extracellular domains of receptor kinases and subsequent activation of the signaling pathway by receptor autophosphorylation. In contrast to this typical scenario, we propose that a putative style ligand transduces the signal in pollen tubes by triggering the specific dephosphorylation of LePRK2, followed by dissociation of the LePRK complex.

L12 ANSWER 5 OF 31 MEDLINE on STN
ACCESSION NUMBER: 2003095377 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12606940
TITLE: Role for RhoB and PRK in the suppression of epithelial cell transformation by farnesyltransferase inhibitors.
AUTHOR: Zeng Ping-Yao; Rane Neena; Du Wei; Chintapalli Janaki; Prendergast George C
CORPORATE SOURCE: The Wistar Institute, Philadelphia, PA 19096, USA.
CONTRACT NUMBER: CA82222 (NCI)
SOURCE: Oncogene, (2003 Feb 27) Vol. 22, No. 8, pp. 1124-34. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 28 Feb 2003
Last Updated on STN: 4 Apr 2003
Entered Medline: 3 Apr 2003

AB Recent genetic investigations have established that RhoB gain-of-function is sufficient to mediate the antitransforming effects of farnesyltransferase inhibitors (FTIs) in H-Ras-transformed fibroblast systems. In this study, we addressed the breadth and mechanism of RhoB action in epithelial cells transformed by oncoproteins which are themselves insensitive to FTI inactivation. Rat intestinal epithelial (RIE) cells transformed by activated K-Ras or Rac1 were highly sensitive to FTI-induced actin reorganization and growth inhibition, despite the inability of FTI to block prenylation of either K-Ras or Rac1. Ectopic expression of the geranylgeranylated RhoB isoform elicited in cells by FTI treatment phenocopied these effects. Analysis of RhoB effector domain mutants pointed to a role for PRK, a Rho effector kinase implicated in the physiological function of RhoB in intracellular receptor trafficking, and these findings were supported further by experiments in a fibroblast system. We propose that FTIs recruit the antioncogenic RhoB protein in the guise of RhoB-GG to interfere with signaling by pro-oncogenic Rho proteins, possibly by sequestering common exchange factors or effectors such as PRK that are important for cell transformation.

L12 ANSWER 6 OF 31 MEDLINE on STN
ACCESSION NUMBER: 2003043428 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12514133
TITLE: A novel inducible transactivation domain in the androgen receptor: implications for PRK in prostate cancer.
AUTHOR: Metzger Eric; Muller Judith M; Ferrari Stefano; Buettner Reinhard; Schule Roland
CORPORATE SOURCE: Universitats-Frauenklinik und Zentrum fur Klinische Forschung, Klinikum der Universitat Freiburg, Breisacherstrasse 66, D-79106 Freiburg, Germany.
SOURCE: The EMBO journal, (2003 Jan 15) Vol. 22, No. 2, pp. 270-80. Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 30 Jan 2003
Last Updated on STN: 26 Feb 2003
Entered Medline: 25 Feb 2003

AB In addition to the classical activation by ligands, nuclear receptor activity is also regulated by ligand-independent signalling. Here, we unravel a novel signal transduction pathway that links the RhoA effector protein kinase C-related kinase PRK1 to the transcriptional activation of the androgen receptor (AR). Stimulation of the PRK signalling cascade results in a ligand-dependent superactivation of AR. We show that AR and PRK1 interact both in vivo and in vitro. The transactivation unit 5 (TAU-5) located in the N-terminus of AR suffices for activation by PRK1. Thus, TAU-5 defines a novel, signal-inducible transactivation domain. Furthermore, PRK1 promotes a functional complex of AR with the co-activator TIF-2. Importantly, PRK signalling also stimulates AR activity in the presence of adrenal androgens, which are still present in prostate tumour patients subjected to testicular androgen ablation therapy. Moreover, PRK1 activates AR even in the presence of the AR antagonist cyproterone acetate that is used in the clinical management of prostate cancer. Since prostate tumours strongly overexpress PRK1, our data support a model in which AR activity is controlled by PRK signalling.

L12 ANSWER 7 OF 31 MEDLINE on STN
ACCESSION NUMBER: 2002730482 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12492480
TITLE: Endogenous mono-ADP-ribosylation mediates smooth muscle cell proliferation and migration via protein kinase N-dependent induction of c-fos expression.
AUTHOR: Yau Lorraine; Litchie Brenda; Thomas Shawn; Storie Benjamin; Yurkova Natalia; Zahradka Peter
CORPORATE SOURCE: Institute of Cardiovascular Sciences, St. Boniface Research Centre and Department of Physiology, University of Manitoba, Winnipeg, MB, Canada.
SOURCE: European journal of biochemistry / FEBS, (2003 Jan) Vol. 270, No. 1, pp. 101-10.
Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 21 Dec 2002
Last Updated on STN: 26 Feb 2003
Entered Medline: 25 Feb 2003

AB ADP-ribosylation has been coupled to intracellular events associated with smooth muscle cell vasoreactivity, cytoskeletal integrity and free radical damage. Additionally, there is evidence that ADP-ribosylation is required for smooth muscle cell proliferation. Our investigation employed selective inhibitors to establish that mono-ADP-ribosylation and not poly(ADP-ribosyl)ation was necessary for the stimulation of DNA synthesis by mitogens. Mitogen treatment increased concomitantly the activity of both soluble and particulate mono-ADP-ribosyltransferase, as well as the number of modified proteins. Inclusion of meta-iodobenzylguanidine (MIBG), a selective decoy substrate of arginine-dependent mono-ADP-ribosylation, prevented the modification of these proteins. MIBG also blocked the stimulation of DNA and RNA synthesis, prevented smooth muscle cell migration and suppressed the induction of c-fos and c-myc gene expression. An examination of relevant signal transduction pathways showed that MIBG did not interfere with MAP kinase and phosphatidylinositol 3-kinase stimulation; however, it did inhibit phosphorylation of the Rho effector, PRK1/2. This novel observation suggests that mono-ADP-ribosylation participates in a Rho- dependent signalling pathway that is required for immediate early gene expression.

L12 ANSWER 8 OF 31 MEDLINE on STN
ACCESSION NUMBER: 2003148179 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12663216
TITLE: On your mark, get set, GROW! LePRK2-LAT52 interactions regulate pollen tube growth.
AUTHOR: Johnson Mark A; Preuss Daphne
CORPORATE SOURCE: Department of Molecular Genetics and Cell Biology, Howard Hughes Medical Institute, The University of Chicago, Erman Biological Center, 1103 E. 57th Street, Chicago, IL 60637, USA.
SOURCE: Trends in plant science, (2003 Mar) Vol. 8, No. 3, pp. 97-9.
Journal code: 9890299. ISSN: 1360-1385.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 31 Mar 2003
Last Updated on STN: 8 Jun 2003
Entered Medline: 6 Jun 2003

AB Recent discoveries show that LAT52 and LePRK2, two pollen-specific

proteins, interact in what might be an autocrine signaling system. This exciting finding indicates that successful fertilization requires ligand-receptor kinase signals that regulate pollen-tube growth. The stage is now set to identify other components of this pathway and to explore their connections with the many signals exchanged between pollen and pistil.

L12 ANSWER 9 OF 31 MEDLINE on STN
ACCESSION NUMBER: 2002622165 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12177059
TITLE: Regulation of kinase activity of 3-phosphoinositide-dependent protein kinase-1 by binding to 14-3-3.
AUTHOR: Sato Saori; Fujita Naoya; Tsuruo Takashi
CORPORATE SOURCE: Institute of Molecular and Cellular Biosciences, The University of Tokyo, Tokyo 113-0032, Japan.
SOURCE: The Journal of biological chemistry, (2002 Oct 18) Vol. 277, No. 42, pp. 39360-7. Electronic Publication: 2002-08-12.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 17 Oct 2002
Last Updated on STN: 5 Jan 2003
Entered Medline: 19 Dec 2002

AB 3-Phosphoinositide-dependent protein kinase-1 (PDK1) plays a central role in activating the protein kinase A, G, and C subfamily. In particular, PDK1 plays an important role in regulating the Akt survival pathway by phosphorylating Akt on Thr-308. PDK1 kinase activity was thought to be constitutively active; however, recent reports suggested that its activity is regulated by binding to other proteins, such as protein kinase C-related kinase-2 (PRK2), p90 ribosomal protein S6 kinase-2 (RSK2), and heat-shock protein 90 (Hsp90). Here we report that PDK1 binds to 14-3-3 proteins in vivo and in vitro through the sequence surrounding Ser-241, a residue that is phosphorylated by itself and is critical for its kinase activity. Mutation of PDK1 to increase its binding to 14-3-3 decreased its kinase activity in vivo. By contrast, mutation of PDK1 to decrease its interaction with 14-3-3 resulted in increased PDK1 kinase activity. Moreover, incubation of wild-type PDK1 with recombinant 14-3-3 in vitro decreased its kinase activity. These data indicate that PDK1 kinase activity is negatively regulated by binding to 14-3-3 through the PDK1 autophosphorylation site Ser-241.

L12 ANSWER 10 OF 31 MEDLINE on STN
ACCESSION NUMBER: 2002457369 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12215520
TITLE: A cysteine-rich extracellular protein, LAT52, interacts with the extracellular domain of the pollen receptor kinase LePRK2.
AUTHOR: Tang Weihua; Ezcurra Ines; Muschietti Jorge; McCormick Sheila
CORPORATE SOURCE: Plant Gene Expression Center, United States Department of Agriculture/Agricultural Research Service, Albany, California 94710, USA.
SOURCE: The Plant cell, (2002 Sep) Vol. 14, No. 9, pp. 2277-87.
Journal code: 9208688. ISSN: 1040-4651.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 7 Sep 2002

Last Updated on STN: 28 Dec 2002
Entered Medline: 27 Dec 2002

AB Pollen germination and pollen tube growth are thought to require extracellular cues, but how these cues are perceived and transduced remains largely unknown. Pollen receptor kinases are plausible candidates for this role; they might bind extracellular ligands and thereby mediate cytoplasmic events required for pollen germination and pollen tube growth. To search for pollen-expressed ligands for pollen receptor kinases, we used the extracellular domains of three pollen-specific receptor kinases of tomato (LePRK1, LePRK2, and LePRK3) as baits in a yeast two-hybrid screen. We identified numerous secreted or plasma membrane-bound candidate ligands. One of these, the Cys-rich protein LAT52, was known to be essential during pollen hydration and pollen tube growth. We used in vivo coimmunoprecipitation to demonstrate that LAT52 was capable of forming a complex with LePRK2 in pollen and to show that the extracellular domain of LePRK2 was sufficient for the interaction. Soluble LAT52 can exist in differently sized forms, but only the larger form can interact with LePRK2. We propose that LAT52 might be a ligand for LePRK2.

L12 ANSWER 11 OF 31 MEDLINE on STN
ACCESSION NUMBER: 2002055627 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11781095
TITLE: Regulation of both PDK1 and the phosphorylation of PKC-zeta and -delta by a C-terminal PRK2 fragment.
AUTHOR: Hodgkinson Conrad P; Sale Graham J
CORPORATE SOURCE: Division of Biochemistry and Molecular Biology, School of Biological Sciences, University of Southampton, Southampton, UK.
SOURCE: Biochemistry, (2002 Jan 15) Vol. 41, No. 2, pp. 561-9. Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 25 Jan 2002
Last Updated on STN: 20 Apr 2002
Entered Medline: 4 Feb 2002

AB The mechanism by which PDK1 regulates AGC kinases remains unclear. To further understand this process, we performed a yeast two-hybrid screen using PDK1 as bait. PKC-zeta, PKC-delta, and PRK2 were identified as interactors of PDK1. A combination of yeast two-hybrid binding assays and coprecipitation from mammalian cells was used to characterize the nature of the PDK1-PKC interaction. The presence of the PH domain of PDK1 inhibited the interaction of PDK1 with the PKCs. A contact region of PDK1 was mapped between residues 314 and 408. The interaction of PDK1 with the PKCs required the full-length PKC-zeta and -delta proteins apart from their C-terminal tails. PDK1 was able to phosphorylate full-length PKC-zeta and -delta but not PKC-zeta and -delta constructs containing the PDK1 phosphorylation site but lacking the C-terminal tails. A C-terminal PRK2 fragment, normally produced by caspase-3 cleavage during apoptosis, inhibited PDK1 autophosphorylation by >90%. The ability of PDK1 to phosphorylate PKC-zeta and -delta in vitro was also markedly inhibited by the PRK2 fragment. Additionally, generation of the PRK2 fragment in vivo inhibited by >90% the phosphorylation of endogenous PKC-zeta by PDK1. In conclusion, these results show that the C-terminal tail of PKC is a critical determinant for PKC-zeta and -delta phosphorylation by PDK1. Moreover, the C-terminal PRK2 fragment acts as a potent negative regulator of PDK1 autophosphorylation and PDK1 kinase activity against PKC-zeta and -delta. As the C-terminal PRK2 fragment is naturally generated during apoptosis, this may provide a mechanism of restraining prosurvival signals during apoptosis.

L12 ANSWER 12 OF 31 MEDLINE on STN
ACCESSION NUMBER: 2002055825 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11777936
TITLE: Fyn tyrosine kinase is a downstream mediator of Rho/ PRK2 function in keratinocyte cell-cell adhesion.
AUTHOR: Calautti Enzo; Grossi Maddalena; Mammucari Cristina; Aoyama Yumi; Pirro Maria; Ono Yoshitaka; Li Jie; Dotto G Paolo
CORPORATE SOURCE: Cutaneous Biology Research Center, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129.
CONTRACT NUMBER: AR39190 (NIAMS)
CA16038 (NCI)
CA73796 (NCI)
SOURCE: The Journal of cell biology, (2002 Jan 7) Vol. 156, No. 1, pp. 137-48. Electronic Publication: 2002-01-03.
Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 25 Jan 2002
Last Updated on STN: 5 Jan 2003
Entered Medline: 14 Feb 2002
AB The Rho GTPase and Fyn tyrosine kinase have been implicated previously in positive control of keratinocyte cell-cell adhesion. Here, we show that Rho and Fyn operate along the same signaling pathway. Endogenous Rho activity increases in differentiating keratinocytes and is required for both Fyn kinase activation and increased tyrosine phosphorylation of beta- and gamma-catenin, which is associated with the establishment of keratinocyte cell-cell adhesion. Conversely, expression of constitutive active Rho is sufficient to promote cell-cell adhesion through a tyrosine kinase- and Fyn-dependent mechanism, trigger Fyn kinase activation, and induce tyrosine phosphorylation of beta- and gamma-catenin and p120ctn. The positive effects of activated Rho on cell-cell adhesion are not induced by an activated Rho mutant with defective binding to the serine/threonine PRK2/PKN kinases. Endogenous PRK2 kinase activity increases with keratinocyte differentiation, and, like activated Rho, increased PRK2 activity promotes keratinocyte cell-cell adhesion and induces tyrosine phosphorylation of beta- and gamma-catenin and Fyn kinase activation. Thus, these findings reveal a novel role of Fyn as a downstream mediator of Rho in control of keratinocyte cell-cell adhesion and implicate the PRK2 kinase, a direct Rho effector, as a link between Rho and Fyn activation.

L12 ANSWER 13 OF 31 MEDLINE on STN
ACCESSION NUMBER: 2001264401 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11356191
TITLE: The protein kinase C-related kinase PRK2 interacts with the protein tyrosine phosphatase PTP-BL via a novel PDZ domain binding motif.
AUTHOR: Gross C; Heumann R; Erdmann K S
CORPORATE SOURCE: Department of Molecular Neurobiochemistry, Ruhr-University Bochum, 44780, Bochum, Germany.
SOURCE: FEBS letters, (2001 May 11) Vol. 496, No. 2-3, pp. 101-4.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 2 Jul 2001
Last Updated on STN: 2 Jul 2001
Entered Medline: 28 Jun 2001
AB Protein tyrosine phosphatase-basophil like (PTP-BL) is a large

non-transmembrane protein tyrosine phosphatase implicated in the modulation of the cytoskeleton. Here we describe a novel interaction of PTP-BL with the protein kinase C-related kinase 2 (PRK2), a serine/threonine kinase regulated by the G-protein rho. This interaction is mediated by the PSD-95, Drosophila discs large, zonula occludens (PDZ)3 domain of PTP-BL and the extreme C-terminus of PRK2 as shown by yeast two-hybrid assays and coimmunoprecipitation experiments from transfected HeLa cells. In particular, we demonstrate that a conserved C-terminal cysteine of PRK2 is indispensable for the interaction with PTP-BL. In HeLa cells we demonstrate colocalization of both proteins in lamellipodia like structures. Interaction of PTP-BL with the rho effector kinase PRK2 gives further evidence for a possible function of PTP-BL in the regulation of the actin cytoskeleton.

L12 ANSWER 14 OF 31 MEDLINE on STN
ACCESSION NUMBER: 2001048392 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10926925
TITLE: Inhibition of Akt and its anti-apoptotic activities by tumor necrosis factor-induced protein kinase C-related kinase 2 (PRK2) cleavage.
AUTHOR: Koh H; Lee K H; Kim D; Kim S; Kim J W; Chung J
CORPORATE SOURCE: Department of Biological Sciences, Korea Advanced Institute of Science and Technology, 373-1 Kusong-Dong, Yusong, Taejon 305-701, Republic of Korea.
SOURCE: The Journal of biological chemistry, (2000 Nov 3) Vol. 275, No. 44, pp. 34451-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 14 Dec 2000

AB Akt is stimulated by several growth factors and has a major anti-apoptotic role in the cell. Therefore, we hypothesized that a pathway leading to the inhibition of Akt might be utilized in the process of apoptosis. Accordingly, we used a yeast two-hybrid screening assay to identify the proteins that interact with and possibly inhibit Akt. We found that the C-terminal region of protein kinase C-related kinase 2 (PRK2), containing amino acids 862 to 908, specifically binds to Akt in yeast and mammalian cells. During early stages of apoptosis, the C-terminal region of PRK2 is cleaved from the inhibitory N-terminal region and can bind Akt. The protein-protein interaction between Akt and the PRK2 C-terminal region specifically down-modulates the protein kinase activities of Akt by inhibiting phosphorylation at threonine 308 and serine 473 of Akt. This inhibition of Akt leads to the inhibition of the downstream signaling of Akt in vivo. The PRK2 C-terminal fragment strongly inhibits the Akt-mediated phosphorylation of BAD, a pro-apoptotic Bcl-2 family protein, and blocks the anti-apoptotic activities of Akt in vivo. These results provide direct evidence that the products of protein cleavage during apoptosis inhibit pro-survival signalings, leading to the amplification of pro-apoptotic signalings in the cell.

L12 ANSWER 15 OF 31 MEDLINE on STN
ACCESSION NUMBER: 2000428384 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10818102
TITLE: MEK kinase 2 binds and activates protein kinase C-related kinase 2. Bifurcation of kinase regulatory pathways at the level of an MAPK kinase kinase.
AUTHOR: Sun W; Vincent S; Settleman J; Johnson G L
CORPORATE SOURCE: Department of Pharmacology, University of Colorado Health

Sciences Center and University of Colorado Cancer Center, Denver, Colorado 80262, USA.
CONTRACT NUMBER: DK37871 (NIDDK)
DK48845 (NIDDK)
GM30324 (NIGMS)
+
SOURCE: The Journal of biological chemistry, (2000 Aug 11) Vol. 275, No. 32, pp. 24421-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 22 Sep 2000
Last Updated on STN: 22 Sep 2000
Entered Medline: 14 Sep 2000

AB MEK kinase 2 (MEKK2) is a 70-kDa protein serine/threonine kinase that has been shown to function as a mitogen-activated protein kinase (MAPK) kinase kinase. MEKK2 has its kinase domain in the COOH-terminal moiety of the protein. The NH(2)-terminal moiety of MEKK2 has no signature motif that would suggest a defined regulatory function. Yeast two-hybrid screening was performed to identify proteins that bind MEKK2. Protein kinase C-related kinase 2 (PRK2) was found to bind MEKK2; PRK2 has been previously shown to bind RhoA and the Src homology 3 domain of Nck. PRK2 did not bind MEKK3, which is closely related to MEKK2. The MEKK2 binding site maps to amino acids 637-660 in PRK2 , which is distinct from the binding sites for RhoA and Nck. This sequence is divergent in the closely related kinase PRK1, which did not bind MEKK2. In cells, MEKK2 and PRK2 are co-immunoprecipitated and PRK2 is activated by MEKK2. Similarly, purified recombinant MEKK2 activated PRK2 in vitro. MEKK2 activation of PRK2 is independent of MEKK2 regulation of the c-Jun NH(2)-terminal kinase pathway. MEKK2 activation of PRK2 results in a bifurcation of signaling for the dual control of MAPK pathways and PRK2 regulated responses.

L12 ANSWER 16 OF 31 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2000396616 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10764742
TITLE: A 3-phosphoinositide-dependent protein kinase-1 (PDK1) docking site is required for the phosphorylation of protein kinase Czeta (PKCzeta) and PKC-related kinase 2 by PDK1.
AUTHOR: Balendran A; Biondi R M; Cheung P C; Casamayor A; Deak M; Alessi D R
CORPORATE SOURCE: MRC Protein Phosphorylation Unit, Division of Signal Transduction Therapy, MSI/WTB Complex, University of Dundee, Dow Street, Dundee DD1 5EH, Scotland, United Kingdom.
SOURCE: The Journal of biological chemistry, (2000 Jul 7) Vol. 275, No. 27, pp. 20806-13.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 24 Aug 2000
Last Updated on STN: 20 Apr 2002
Entered Medline: 16 Aug 2000

AB Members of the AGC subfamily of protein kinases including protein kinase B, p70 S6 kinase, and protein kinase C (PKC) isoforms are activated and/or stabilized by phosphorylation of two residues, one that resides in the

T-loop of the kinase domain and the other that is located C-terminal to the kinase domain in a region known as the hydrophobic motif. Atypical PKC isoforms, such as PKCzeta, and the PKC-related kinases, like PRK2, are also activated by phosphorylation of their T-loop site but, instead of possessing a phosphorylatable Ser/Thr in their hydrophobic motif, contain an acidic residue. The 3-phosphoinositide-dependent protein kinase (PDK1) activates many members of the AGC subfamily of kinases in vitro, including PKCzeta and PRK2 by phosphorylating the T-loop residue. In the present study we demonstrate that the hydrophobic motifs of PKCzeta and PKCiota, as well as PRK1 and PRK2, interact with the kinase domain of PDK1. Mutation of the conserved residues of the hydrophobic motif of full-length PKCzeta, full-length PRK2, or PRK2 lacking its N-terminal regulatory domain abolishes or significantly reduces the ability of these kinases to interact with PDK1 and to become phosphorylated at their T-loop sites in vivo. Furthermore, overexpression of the hydrophobic motif of PRK2 in cells prevents the T-loop phosphorylation and thus inhibits the activation of PRK2 and PKCzeta. These findings indicate that the hydrophobic motif of PRK2 and PKCzeta acts as a "docking site" enabling the recruitment of PDK1 to these substrates. This is essential for their phosphorylation by PDK1 in cells.

L12 ANSWER 17 OF 31 MEDLINE on STN
ACCESSION NUMBER: 2000305289 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10843871
TITLE: The Rho effector, PKN, regulates ANF gene transcription in cardiomyocytes through a serum response element.
AUTHOR: Morissette M R; Sah V P; Glembotski C C; Brown J H
CORPORATE SOURCE: Department of Pharmacology and Graduate Program in Biomedical Sciences, University of California, San Diego, La Jolla, 92093, USA.
CONTRACT NUMBER: HL-28143 (NHLBI)
HL-46345 (NHLBI)
SOURCE: American journal of physiology. Heart and circulatory physiology, (2000 Jun) Vol. 278, No. 6, pp. H1769-74. Journal code: 100901228. ISSN: 0363-6135.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20 Jul 2000
Last Updated on STN: 20 Apr 2002
Entered Medline: 13 Jul 2000

AB The low-molecular-weight GTP-binding protein RhoA mediates hypertrophic growth and atrial natriuretic factor (ANF) gene expression in neonatal rat ventricular myocytes. Neither the effector nor the promoter elements through which Rho exerts its regulatory effects on ANF gene expression have been elucidated. When constitutively activated forms of Rho kinase and two protein kinase C-related kinases, PKN (PRK1) and PRK2, were compared, only PKN generated a robust stimulation of a luciferase reporter gene driven by a 638-bp fragment on the ANF promoter. This ANF promoter fragment contains a proximal serum response element (SRE) and an Sp-1-like element required for the transcriptional response to phenylephrine (PE). This response was inhibited by dominant negative Rho. The ability of dominant negative Rho to inhibit the response to PE and the ability of PKN to stimulate ANF reporter gene expression were both lost when the SRE was mutated. Mutation of the Sp-1-like element also attenuated the response to PKN. A minimal promoter driven by ANF SRE sequences was sufficient to confer Rho- and PKN-mediated gene expression. Interestingly, PKN preferentially stimulated the ANF versus the c-fos SRE reporter gene. Thus PKN and Rho are able to regulate transcriptional activation of the ANF SRE by a common element that could implicate PKN as

a downstream effector of Rho in transcriptional responses associated with hypertrophy.

L12 ANSWER 18 OF 31 MEDLINE on STN
ACCESSION NUMBER: 2000164465 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10698939
TITLE: Identification of a pocket in the PDK1 kinase domain that interacts with PIF and the C-terminal residues of PKA.
AUTHOR: Biondi R M; Cheung P C; Casamayor A; Deak M; Currie R A; Alessi D R
CORPORATE SOURCE: Divison of Signal Transduction Therapy, MSI/WTB Complex, University of Dundee, Dow Street, Dundee DD1 5EH, UK.. rbiondi@bad.dundee.ac.uk
SOURCE: The EMBO journal, (2000 Mar 1) Vol. 19, No. 5, pp. 979-88. Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 5 May 2000
Last Updated on STN: 20 Apr 2002
Entered Medline: 26 Apr 2000

AB The 3-phosphoinositide-dependent protein kinase-1 (PDK1) phosphorylates and activates a number of protein kinases of the AGC subfamily. The kinase domain of PDK1 interacts with a region of protein kinase C-related kinase-2 (PRK2), termed the PDK1-interacting fragment (PIF), through a hydrophobic motif. Here we identify a hydrophobic pocket in the small lobe of the PDK1 kinase domain, separate from the ATP- and substrate-binding sites, that interacts with PIF. Mutation of residues predicted to form part of this hydrophobic pocket either abolished or significantly diminished the affinity of PDK1 for PIF. PIF increased the rate at which PDK1 phosphorylated a synthetic dodecapeptide (T308tide), corresponding to the sequences surrounding the PDK1 phosphorylation site of PKB. This peptide is a poor substrate for PDK1, but a peptide comprising T308tide fused to the PDK1-binding motif of PIF was a vastly superior substrate for PDK1. Our results suggest that the PIF-binding pocket on the kinase domain of PDK1 acts as a 'docking site', enabling it to interact with and enhance the phosphorylation of its substrates.

L12 ANSWER 19 OF 31 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2001061082 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11078882
TITLE: Further evidence that 3-phosphoinositide-dependent protein kinase-1 (PDK1) is required for the stability and phosphorylation of protein kinase C (PKC) isoforms.
AUTHOR: Balendran A; Hare G R; Kieloch A; Williams M R; Alessi D R
CORPORATE SOURCE: MRC Protein Phosphorylation, MSI/WTB complex, University of Dundee, Dow Street, DD1 5EH, Dundee, UK.
SOURCE: FEBS letters, (2000 Nov 10) Vol. 484, No. 3, pp. 217-23. Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 20 Apr 2002
Entered Medline: 22 Dec 2000

AB The multi-site phosphorylation of the protein kinase C (PKC) superfamily plays an important role in the regulation of these enzymes. One of the key phosphorylation sites required for the activation of all PKC isoforms lies in the T-loop of the kinase domain. Recent in vitro and transfection experiments indicate that phosphorylation of this residue can be mediated

by the 3-phosphoinositide-dependent protein kinase-1 (PDK1). In this study, we demonstrate that in embryonic stem (ES) cells lacking PDK1 (PDK1-/- cells), the intracellular levels of endogenously expressed PKCalpha, PKCbetaI, PKCgamma, PKCdelta, PKCepsilon, and PKC-related kinase-1 (PRK1) are vastly reduced compared to control ES cells (PDK1+/+ cells). The levels of PKCzeta and PRK2 protein are only moderately reduced in the PDK1-/- ES cells. We demonstrate that in contrast to PKCzeta expressed PDK1+/+ ES cells, PKCzeta in ES cells lacking PDK1 is not phosphorylated at its T-loop residue. This provides the first genetic evidence that PKCzeta is a physiological substrate for PDK1. In contrast, PRK2 is still partially phosphorylated at its T-loop in PDK1-/- cells, indicating the existence of a PDK1-independent mechanism for the phosphorylation of PRK2 at this residue.

L12 ANSWER 20 OF 31 MEDLINE on STN
ACCESSION NUMBER: 2001111093 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11112322
TITLE: Protein kinase C-related kinase 2 phosphorylates the protein synthesis initiation factor eIF4E in starfish oocytes.
AUTHOR: Lee S J; Stapleton G; Greene J H; Hille M B
CORPORATE SOURCE: Department of Zoology and Center for Developmental Biology, University of Washington, Seattle, Washington 98195, USA.
SOURCE: Developmental biology, (2000 Dec 15) Vol. 228, No. 2, pp. 166-80.
Journal code: 0372762. ISSN: 0012-1606.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 2 Feb 2001

AB Phosphorylation of eIF4E is required for protein synthesis during starfish oocyte maturation. The activity of protein kinase C-related kinase 2 (PRK2) increases prior to the phosphorylation of eIF4E (G. Stapleton et al., 1998, Dev. Biol. 193, 34-46). We investigate here whether eIF4E is activated by PRK2. A 3.5-kb eIF4E clone isolated from starfish cDNA is 57% identical to human eIF4E and contains the putative phosphorylation site serine-209. The serine-209 environment (SKTGS(209)MAKSRF) is similar to the consensus sequence of the phosphorylation site of protein kinase C and related kinases. A starfish eIF4E fusion protein (GST-4E) was phosphorylated in vitro by PRK2 in the presence of 1,2-diolyl-sn-glycerol 3-phosphate. In contrast, replacing the GST-4E serine-209 with an alanine significantly reduced this phosphorylation. Analysis by two-dimensional phosphopeptide mapping reveals a major phosphopeptide in trypsin-digested GST-4E, but not in its serine-209 mutant. Importantly, this major phosphopeptide in GST-4E corresponds to a major phosphopeptide of eIF4E isolated from (32)P-labeled oocytes. Thus, PRK2 may regulate translation initiation during oocyte maturation by phosphorylating the serine-209 residue of eIF4E in starfish. We also demonstrate that high levels of cAMP inhibit the activation of PRK2, eIF4E, and the eIF4E binding protein during starfish oocyte maturation, while PI3 kinase activates these proteins. Copyright 2000 Academic Press.

L12 ANSWER 21 OF 31 MEDLINE on STN
ACCESSION NUMBER: 1999143109 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9988689
TITLE: Loop 6 of RhoA confers specificity for effector binding, stress fiber formation, and cellular transformation.
AUTHOR: Zong H; Raman N; Mickelson-Young L A; Atkinson S J;

Quilliam L A
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, Indiana 46202, USA.
SOURCE: The Journal of biological chemistry, (1999 Feb 19) Vol. 274, No. 8, pp. 4551-60.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 26 Mar 1999
Last Updated on STN: 20 Apr 2002
Entered Medline: 18 Mar 1999

AB Rho family GTPases regulate multiple cellular processes, including cytoskeletal organization, gene expression, and transformation. These effects are achieved through the interaction of GTP-bound proteins with various downstream targets. A series of RhoA/Rac1 and Rho/Ras chimeras was generated to map the domain(s) of RhoA involved in its association with two classes of effector kinase, represented by PRK2 and ROCK-I. Although the switch 1 domain was required for effector binding, the N terminus of Rho (residues 1-75) was interchangeable with that of Rac. This suggested that the region of Rho that confers effector binding specificity lay further C-terminal. Subsequent studies indicated that the "insert domain"(residues 123-137), a region unique to Rho family GTPases, is not the specificity determinant. However, a determinant for effector binding was identified between Rho residues 75-92. Rac to Rho point mutations (V85D or A88D) within loop 6 of Rac promoted its association with PRK2 and ROCK, whereas the reciprocal Rho(D87V/D90A) double mutant significantly reduced effector binding capacity. In vivo studies showed that microinjection of Rac(Q6IL/V85D/A88D) but not Rac(Q6IL) induced stress fiber formation in LLC-PK epithelial cells, suggesting that loop 6 residues conferred the ability of Rac to activate ROCK. On the other hand, the reciprocal Rho (Q6IL/D87V/D90A) mutant was defective in its ability to transform NIH 3T3 cells. These data suggest that although Rho effectors can utilize a Rho or Rac switch 1 domain to sense the GTP-bound state of Rho, unique residues within loop 6 are essential for determining both effector binding specificity and cellular function.

L12 ANSWER 22 OF 31 MEDLINE on STN
ACCESSION NUMBER: 1999398425 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10467162
TITLE: Mutational analysis of the regulatory mechanism of PKN: the regulatory region of PKN contains an arachidonic acid-sensitive autoinhibitory domain.
AUTHOR: Yoshinaga C; Mukai H; Toshimori M; Miyamoto M; Ono Y
CORPORATE SOURCE: Graduate School of Science and Technology Faculty of Science, Kobe University, Kobe, 657-8501, Japan.
SOURCE: Journal of biochemistry, (1999 Sep) Vol. 126, No. 3, pp. 475-84.
Journal code: 0376600. ISSN: 0021-924X.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 29 Feb 2000
Last Updated on STN: 29 Feb 2000
Entered Medline: 11 Feb 2000

AB PKN is a fatty acid- and Rho GTPase-activated protein kinase whose catalytic domain in the carboxyl terminus is homologous to those of protein kinase C (PKC) family members. The amino terminal region of PKN is suggested to function as a regulatory domain, since tryptic cleavage or

the binding of Rho GTPase to this region results in protein kinase activation of PKN. The structural basis for the regulation of PKN was investigated by analyzing the activity of a series of deletion/site-directed mutants expressed in insect cells. The amino-terminally truncated form of PKN (residue 455-942) showed low basal activity similar to that of the wild-type enzyme, and was arachidonic acid-dependent. However, further deletion (residue 511-942) resulted in a marked increase in the basal activity and a decrease in the arachidonic acid dependency. A (His)(6)-tagged protein comprising residues 455-511 of PKN (designated His-Ialpha) inhibited the kinase activity of the catalytic fragment of PKN in a concentration-dependent manner in competition with substrate (K(i) = 0.6+/-0.2 microM). His-Ialpha also inhibited the activity of the catalytic fragment of PRK2, an isoform of PKN, but had no inhibitory effect on protein kinase A or protein kinase Cdelta. The IC(50) value obtained in the presence of 40 microM arachidonic acid was two orders of magnitude greater than that in the absence of the modifier. These results indicate that this protein fragment functions as a specific inhibitor of PKN and PRK2, and that arachidonic acid relieves the catalytic activity of wild-type PKN from autoinhibition by residues 455-511 of PKN. Autophosphorylation of wild-type PKN increased the protein kinase activity, however, substitution of Thr64, Ser374, or Thr531 in the regulatory region of PKN with alanine, abolished this effect. Substitution of Thr774 in the activation loop of the catalytic domain of PKN with alanine completely abolished the protein kinase activity. These results suggest that these phosphorylation sites are also important in the regulation of the PKN kinase activity. Potential differences in the mechanism of activation between the catalytic regions of PKN and PRK2 are also discussed.

L12 ANSWER 23 OF 31 MEDLINE on STN
ACCESSION NUMBER: 1999244939 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10226025
TITLE: PDK1 acquires PDK2 activity in the presence of a synthetic peptide derived from the carboxyl terminus of PRK2
.
AUTHOR: Balendran A; Casamayor A; Deak M; Paterson A; Gaffney P; Currie R; Downes C P; Alessi D R
CORPORATE SOURCE: MRC Protein Phosphorylation Unit, Department of Biochemistry, University of Dundee, Dundee DD1 5EH, UK.
SOURCE: Current biology : CB, (1999 Apr 22) Vol. 9, No. 8, pp. 393-404.
Journal code: 9107782. ISSN: 0960-9822.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 14 Jun 1999
Last Updated on STN: 20 Apr 2002
Entered Medline: 1 Jun 1999

AB BACKGROUND: Protein kinase B (PKB) is activated by phosphorylation of Thr308 and of Ser473. Thr308 is phosphorylated by the 3-phosphoinositide-dependent protein kinase-1 (PDK1) but the identity of the kinase that phosphorylates Ser473 (provisionally termed PDK2) is unknown. RESULTS: The kinase domain of PDK1 interacts with a region of protein kinase C-related kinase-2 (PRK2), termed the PDK1-interacting fragment (PIF). PIF is situated carboxy-terminal to the kinase domain of PRK2, and contains a consensus motif for phosphorylation by PDK2 similar to that found in PKBalpha, except that the residue equivalent to Ser473 is aspartic acid. Mutation of any of the conserved residues in the PDK2 motif of PIF prevented interaction of PIF with PDK1. Remarkably, interaction of PDK1 with PIF, or with a synthetic peptide encompassing the PDK2 consensus sequence of PIF, converted PDK1 from an enzyme that could phosphorylate only Thr308 of PKBalpha to one

that phosphorylates both Thr308 and Ser473 of PKBalpha in a manner dependent on phosphatidylinositol (3,4,5) trisphosphate (PtdIns(3,4,5)P3). Furthermore, the interaction of PIF with PDK1 converted the PDK1 from a form that is not directly activated by PtdIns(3,4,5)P3 to a form that is activated threefold by PtdIns(3,4,5)P3. We have partially purified a kinase from brain extract that phosphorylates Ser473 of PKBalpha in a PtdIns(3,4,5)P3-dependent manner and that is immunoprecipitated with PDK1 antibodies. CONCLUSIONS: PDK1 and PDK2 might be the same enzyme, the substrate specificity and activity of PDK1 being regulated through its interaction with another protein(s). PRK2 is a probable substrate for PDK1.

L12 ANSWER 24 OF 31 MEDLINE on STN
ACCESSION NUMBER: 1998426194 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9751706
TITLE: Proteolytic activation of PKN by caspase-3 or related protease during apoptosis.
AUTHOR: Takahashi M; Mukai H; Toshimori M; Miyamoto M; Ono Y
CORPORATE SOURCE: Department of Biology, Faculty of Science, Kobe University, Kobe 657-8501, Japan.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1998 Sep 29) Vol. 95, No. 20, pp. 11566-71.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 29 Oct 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 22 Oct 1998

AB PKN, a fatty acid- and Rho-activated serine/threonine kinase having a catalytic domain highly homologous to protein kinase C (PKC), was cleaved at specific sites in apoptotic Jurkat and U937 cells on Fas ligation and treatment with staurosporin or etoposide, respectively. The cleavage of PKN occurred with a time course similar to that of PKCdelta, a known caspase substrate. This proteolysis was inhibited by a caspase inhibitor, acetyl-Asp-Glu-Val-Asp-aldehyde. The cleavage fragments were generated in vitro from PKN by treatment with recombinant caspase-3. Site-directed mutagenesis of specific aspartate residues prevented the appearance of these fragments. These results indicate that PKN is cleaved by caspase-3 or related protease during apoptosis. The major proteolysis took place between the amino-terminal regulatory domain and the carboxyl-terminal catalytic domain, and it generated a constitutively active kinase fragment. The cleavage of PKN may contribute to signal transduction, eventually leading to apoptosis.

L12 ANSWER 25 OF 31 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:605189 HCAPLUS
DOCUMENT NUMBER: 129:199615
TITLE: Structure and function of PKN
AUTHOR(S): Mukai, Hideyuki; Ono, Yoshitaka
CORPORATE SOURCE: Fac. Sci., Kobe Univ., Kobe, 657-8501, Japan
SOURCE: Tanpakushitsu Kakusan Koso (1998), 43(12), 1659-1665
CODEN: TAKKAJ; ISSN: 0039-9450
PUBLISHER: Kyoritsu Shuppan
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review with 39 refs., on (1) structure and expression of a novel protein kinase, PKN, (2) effects of lipids, G-protein Rho, proteolysis, and phosphorylation on the PKN activities, (3) PKN binding to neurofilaments, α-actinin, and PCD17 antigens, (4) involvement of PKN in apoptosis, (5) involvement of PKN in the pathogenesis of Alzheimer's disease, (6)

mapping of PKN gene (PRKCL1), and (7) property and functions of PKN isoform (PKC related kinase 2; PRK2).

L12 ANSWER 26 OF 31 MEDLINE on STN
ACCESSION NUMBER: 1998133989 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9466886
TITLE: Phosphorylation of protein kinase C-related kinase PRK2 during meiotic maturation of starfish oocytes.
AUTHOR: Stapleton G; Nguyen C P; Lease K A; Hille M B
CORPORATE SOURCE: Department of Zoology, University of Washington, Seattle 98195-1800, USA.
SOURCE: Developmental biology, (1998 Jan 1) Vol. 193, No. 1, pp. 36-46.
Journal code: 0372762. ISSN: 0012-1606.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF035554
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 12 Mar 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 4 Mar 1998
AB The resumption of meiosis in the developing starfish oocyte is the result of intracellular signaling events initiated by 1-methyladenine stimulation. One of the earliest detectable kinase activities during meiotic maturation of starfish oocytes is a protein kinase C or PKC-like activity. In this study, several isoforms of protein kinase C were cloned from the oocyte; however, the most abundant PKC-like maternal transcript corresponds to protein kinase C-related kinase 2 (PRK2). PRK2 is expressed in the immature oocyte and at least until germinal vesicle breakdown. Subcellular localization of PRK2 revealed a cytoplasmic distribution in the immature oocyte, which, during meiotic maturation, remained in the cytoplasm but also localized to the disintegrating germinal vesicle. Significantly, PRK2 is phosphorylated in vivo in response to 1-methyladenine which precedes MPF activation, making PRK2 a candidate regulator of early signaling events of meiotic maturation.

L12 ANSWER 27 OF 31 MEDLINE on STN
ACCESSION NUMBER: 1998037762 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9368003
TITLE: Specific proteolysis of the kinase protein kinase C-related kinase 2 by caspase-3 during apoptosis. Identification by a novel, small pool expression cloning strategy.
AUTHOR: Cryns V L; Byun Y; Rana A; Mellor H; Lustig K D; Ghanem L; Parker P J; Kirschner M W; Yuan J
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: AG12859-01 (NIA)
GM26875 (NIGMS)
K08-CA01752-04 (NCI)
SOURCE: The Journal of biological chemistry, (1997 Nov 21) Vol. 272, No. 47, pp. 29449-53.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF027183
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 9 Jan 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 23 Dec 1997

AB The caspase family of proteases plays a critical role in the execution of apoptosis. However, efforts to decipher the molecular mechanisms by which caspases induce cell death have been greatly hindered by the lack of systematic and broadly applicable strategies to identify their substrates. Here we describe a novel expression cloning strategy to rapidly isolate cDNAs encoding caspase substrates that are cleaved during apoptosis. Small cDNA pools (approximately 100 clones each) are transcribed/translated in vitro in the presence of [35S]methionine; these labeled protein pools are then incubated with cytosolic extracts from control and apoptotic cells. cDNA pools encoding proteins that are specifically cleaved by the apoptotic extract and whose cleavage is prevented by the caspase inhibitor acetyl-Tyr-Val-Ala-Asp chloromethylketone are subdivided and retested until a single cDNA is isolated. Using this approach, we isolated a partial cDNA encoding protein kinase C-related kinase 2 (PRK2), a serine-threonine kinase, and demonstrate that full-length human PRK2 is proteolyzed by caspase-3 at Asp117 and Asp700 in vitro. In addition, PRK2 is cleaved rapidly during Fas- and staurosporine-induced apoptosis in vivo by caspase-3 or a closely related caspase. Both of the major apoptotic cleavage sites of PRK2 in vivo lie within its regulatory domain, suggesting that its activity may be deregulated by proteolysis.

L12 ANSWER 28 OF 31 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 97248559 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9092545
TITLE: Isolation and characterization of a structural homologue of human PRK2 from rat liver. Distinguishing substrate and lipid activator specificities.
AUTHOR: Yu W; Liu J; Morrice N A; Wettenhall R E
CORPORATE SOURCE: Russell Grimwade School of Biochemistry and Molecular Biology, University of Melbourne, Parkville, Victoria, 3052, Australia.
SOURCE: The Journal of biological chemistry, (1997 Apr 11) Vol. 272, No. 15, pp. 10030-4.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U75358
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 23 May 1997
Last Updated on STN: 23 May 1997
Entered Medline: 15 May 1997

AB A homologue of human protein kinase C (PKC)-related kinase-2, PRK2, which had previously escaped identification in normal mammalian tissues, was isolated from rat liver as the protease-activated kinase (PAK) originally named PAK-2. The 130-kDa cytosolic enzyme was purified to homogeneity and shown by tryptic peptide and reverse transcriptase- polymerase chain reaction (RT-PCR)-amplified rat cDNA sequence analyses to be structurally related to the 116-kDa rat hepatic PAK-1/protein kinase N (PKN) and, even more closely (95% sequence identity) to the 130-kDa human PKC-related kinase, PRK2. Rat myeloma RNA was used as the RT-PCR template because of its relative abundance in PAK-2/PRK2 mRNA compared with liver and other rat tissues. The catalytic properties of PAK-2/PRK2 in many respects resembled those of hepatic PAK-1/PKN, but were distinguished by more favorable kinetics with several peptide substrates, and greater sensitivity to PKC pseudosubstrate and polybasic amino acid inhibitors. PAK-2/PRK2 was also activated by lipids, particularly cardiolipin and to a lesser extent by other acidic phospholipids and unsaturated fatty acids. Cardiolipin activation was most evident with autophosphorylation and histone H2B phosphorylation, but

only marginally evident with the favored ribosomal S6-(229-239) peptide substrate for the protease-activated kinase activity. It was concluded that PAK-2 is the rat homologue of human PRK2, with biochemical properties distinct from although overlapping those of the PAK-1/PKN/PRK1 isoform.

L12 ANSWER 29 OF 31 MEDLINE on STN
ACCESSION NUMBER: 97220017 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9121475
TITLE: The PRK2 kinase is a potential effector target of both Rho and Rac GTPases and regulates actin cytoskeletal organization.
AUTHOR: Vincent S; Settleman J
CORPORATE SOURCE: Massachusetts General Hospital Cancer Center and Harvard Medical School, Charlestown 02129, USA.
CONTRACT NUMBER: CA62142-02 (NCI)
SOURCE: Molecular and cellular biology, (1997 Apr) Vol. 17, No. 4, pp. 2247-56.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 6 May 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 24 Apr 1997

AB The Ras-related Rho family GTPases mediate signal transduction pathways that regulate a variety of cellular processes. Like Ras, the Rho proteins (which include Rho, Rac, and CDC42) interact directly with protein kinases, which are likely to serve as downstream effector targets of the activated GTPase. Activated RhoA has recently been reported to interact directly with several protein kinases, p120 PKN, p150 ROK alpha and -beta, p160 ROCK, and p164 Rho kinase. Here, we describe the purification of a novel Rho-associated kinase, p140, which appears to be the major Rho-associated kinase activity in most tissues. Peptide microsequencing revealed that p140 is probably identical to the previously reported PRK2 kinase, a close relative of PKN. However, unlike the previously described Rho-binding kinases, which are Rho specific, p140 associates with Rac as well as Rho. Moreover, the interaction of p140 with Rho in vitro is nucleotide independent, whereas the interaction with Rac is completely GTP dependent. The association of p140 with either GTPase promotes kinase activity substantially, and expression of a kinase-deficient form of p140 in microinjected fibroblasts disrupts actin stress fibers. These results indicate that p140 may be a shared kinase target of both Rho and Rac GTPases that mediates their effects on rearrangements of the actin cytoskeleton.

L12 ANSWER 30 OF 31 MEDLINE on STN
ACCESSION NUMBER: 97067117 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8910519
TITLE: Isolation of a NCK-associated kinase, PRK2, an SH3-binding protein and potential effector of Rho protein signaling.
AUTHOR: Quilliam L A; Lambert Q T; Mickelson-Young L A; Westwick J K; Sparks A B; Kay B K; Jenkins N A; Gilbert D J; Copeland N G; Der C J
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology and the Walther Oncology Center, Indiana University School of Medicine, Indianapolis, Indiana 46202, USA..
lawrence_quilliam@iucc.iupui.edu
CONTRACT NUMBER: CA42978 (NCI)
CA52072 (NCI)
CA63139 (NCI)

+

SOURCE: The Journal of biological chemistry, (1996 Nov 15) Vol. 271, No. 46, pp. 28772-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 7 Jan 1997

AB The NCK adapter protein is comprised of three consecutive Src homology 3 (SH3) protein-protein interaction domains and a C-terminal SH2 domain. Although the association of NCK with activated receptor protein-tyrosine kinases, via its SH2 domain, implicates NCK as a mediator of growth factor-induced signal transduction, little is known about the pathway(s) downstream of NCK recruitment. To identify potential downstream effectors of NCK we screened a bacterial expression library to isolate proteins that bind its SH3 domains. Two molecules were isolated, the Wiskott-Aldrich syndrome protein (WASP, a putative CDC42 effector) and a serine/threonine protein kinase (PRK2, closely related to the putative Rho effector PKN). Using interspecific backcross analysis the Prk2 gene was mapped to mouse chromosome 3. Unlike WASP, which bound the SH3 domains of several signaling proteins, PRK2 specifically bound to the middle SH3 domain of NCK and (weakly) that of phospholipase Cgamma. PRK2 also specifically bound to Rho in a GTP-dependent manner and cooperated with Rho family proteins to induce transcriptional activation via the serum response factor. These data suggest that PRK2 may coordinately mediate signal transduction from activated receptor protein-tyrosine kinases and Rho and that NCK may function as an adapter to connect receptor-mediated events to Rho protein signaling.

L12 ANSWER 31 OF 31 MEDLINE on STN
ACCESSION NUMBER: 95154310 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7851406
TITLE: Cloning and expression patterns of two members of a novel protein-kinase-C-related kinase family.
AUTHOR: Palmer R H; Ridden J; Parker P J
CORPORATE SOURCE: Protein Phosphorylation Laboratory, Imperial Cancer Research Fund, London, England.
SOURCE: European journal of biochemistry / FEBS, (1995 Jan 15) Vol. 227, No. 1-2, pp. 344-51.
Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-S75546; GENBANK-S75548; GENBANK-U33052; GENBANK-U33053
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 22 Mar 1995
Last Updated on STN: 15 Mar 1996
Entered Medline: 13 Mar 1995

AB The cDNA clones for two members of a novel protein kinase family were isolated and sequenced. These protein-kinase-C-related kinases, PRK1 and PRK2, display extensive identity to each other, revealing non-kinase domain similar regions. HR1 and HR2. HR1 contains a motif repeated three times (HR1a-c), while HR2 shows similarity to the amino-terminal sequence of protein-kinase-C epsilon and eta isotypes. Both PRK1 and PRK2, expressed in COS 1 cells, are autophosphorylated in immunoprecipitates, indicating intrinsic kinase activity. PRK1 and PRK2, as well as a third member of this family, PRK3, show distinct patterns of expression in adult tissues.

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=> d his

     (FILE 'HOME' ENTERED AT 10:08:25 ON 28 JUL 2006)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 10:08:53 ON 28 JUL 2006
L1         67106 S PHOSPHOINOSITIDE
L2         19704 S L1 (2W) KINASE##
L3          2205 S PDK1
L4         20665 S L2 OR L3
L5           319 S PRK2
L6            60 S L4 AND L5
L7            27 DUP REM L6 (33 DUPLICATES REMOVED)
L8            12 S L5 AND PIF
L9             3 DUP REM L8 (9 DUPLICATES REMOVED)
L10          346 S PKC (W)RELATED
L11           43 S L5 AND L10
L12           31 DUP REM L11 (12 DUPLICATES REMOVED)

=> s PDK2 and l5
L13          18 PDK2 AND L5

=> dup rem l13
PROCESSING COMPLETED FOR L13
L14           8 DUP REM L13 (10 DUPLICATES REMOVED)

=> d 1-8 ibib ab

L14  ANSWER 1 OF 8  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2005:1314312  HCAPLUS
DOCUMENT NUMBER:          144:68264
TITLE:                    Minimal common regions in chromosomes showing changes
                          in copy number in cancers and their use in the
                          diagnosis, prevention, and treatment
INVENTOR(S):              Chin, Lynda
PATENT ASSIGNEE(S):       Dana-Farber Cancer Institute, Inc., USA
SOURCE:                   PCT Int. Appl., 152 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2005118869         A2    20051215    WO 2005-US18850         20050527
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ,
             LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA,
             NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK,
             SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,
             ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
             RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                       US 2004-575795P     P  20040528
                                             US 2004-580337P     P  20040615
AB   Small chromosomal regions, minimal common regions (MCRs) that show a
     change in copy number in neoplastic tissue are identified for use in the
```

early diagnosis of cancer and as markers in the prevention and treatment of the disease.

L14 ANSWER 2 OF 8 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004501625 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15470109
TITLE: Differential roles of PDK1- and PDK2 -phosphorylation sites in the yeast AGC kinases Ypk1, Pkc1 and Sch9.
AUTHOR: Roelants Francoise M; Torrance Pamela D; Thorner Jeremy
CORPORATE SOURCE: Department of Molecular and Cell Biology, Division of Biochemistry and Molecular Biology, University of California, Berkeley, CA 94720-3202, USA.
CONTRACT NUMBER: CA09041 (NCI)
GM07232 (NIGMS)
GM21841 (NIGMS)
SOURCE: Microbiology (Reading, England), (2004 Oct) Vol. 150, No. Pt 10, pp. 3289-304.
Journal code: 9430468. ISSN: 1350-0872.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200501
ENTRY DATE: Entered STN: 8 Oct 2004
Last Updated on STN: 14 Jan 2005
Entered Medline: 13 Jan 2005

AB Saccharomyces cerevisiae Pkh1 and Pkh2 (orthologues of mammalian protein kinase, PDK1) are functionally redundant. These kinases activate three AGC family kinases involved in the maintenance of cell wall integrity: Ypk1 and Ypk2, two closely related, functionally redundant enzymes (orthologues of mammalian protein kinase SGK), and Pkc1 (orthologue of mammalian protein kinase PRK2). Pkh1 and Pkh2 activate Ypk1, Ypk2 and Pkc1 by phosphorylating a Thr in a conserved sequence motif (PDK1 site) within the activation loop of these proteins. A fourth protein kinase involved in growth control and stress response, Sch9 (orthologue of mammalian protein kinase c-Akt/PKB), also carries the conserved activation loop motif. Like other AGC family kinases, Ypk1, Ypk2, Pkc1 and Sch9 also carry a second conserved sequence motif situated in a region C-terminal to the catalytic domain, called the hydrophobic motif (PDK2 site). Currently, there is still controversy surrounding the identity of the enzyme responsible for phosphorylating this second site and the necessity for phosphorylation at this site for in vivo function. Here, genetic and biochemical methods have been used to investigate the physiological consequences of phosphorylation at the PDK1 and PDK2 sites of Ypk1, Pkc1 and Sch9. It was found that phosphorylation at the PDK1 site in the activation loop is indispensable for the essential functions of all three kinases in vivo, whereas phosphorylation at the PDK2 motif plays a non-essential and much more subtle role in modulating the ability of these kinases to regulate the downstream processes in which they participate.

L14 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2003:187088 HCAPLUS
DOCUMENT NUMBER: 138:219710
TITLE: Differentially expressed gene expression profiles in human glomerular diseases
INVENTOR(S): Munger, William E.; Falk, Ronald; Sun, Hongwei; Sasai, Hitoshi; Waga, Iwao; Yamamoto, Jun
PATENT ASSIGNEE(S): Gene Logic, Inc., USA; University of North Carolina At Chapel Hill
SOURCE: PCT Int. Appl., 781 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003016476	A2	20030227	WO 2002-XE25766	20020814
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2003016476	A2	20030227	WO 2002-US25766	20020814
WO 2003016476	A3	20030508		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2001-311837P P 20010814
WO 2002-US25766 A 20020814

AB The present invention is based on the elucidation of global changes in gene expression in peripheral blood leukocytes (PBL) of patients with glomerular diseases exhibiting different types of clin. and pathol. features of glomerular nephropathy as compared to normal PBL as well as the identification of individual genes that are differently expressed in PBL of patients with glomerular diseases. The genes and gene expression information may be used as markers for the diagnosis of disease subtype, such as IgA nephropathy, Minimal Change nephrotic syndrome, antineutrophil cytoplasmic antibody-associated glomerulonephritis (ANCA), focal segmental glomerulosclerosis (FSGS), and lupus nephritis. The genes may also be used as markers to evaluate the effects of a candidate drug or agent on tissues, including PBLs, particularly PBLs undergoing activation or PBLs from a patient with glomerular disease. Differential expression of genes between PBLs from patients with glomerular disease and normal PBL samples was determined using the Affymetrix 42K human gene chip set. [This abstract record is one of nine records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L14 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:875393 HCAPLUS
DOCUMENT NUMBER: 139:363045
TITLE: Genes expressed in atherosclerotic tissue and their use in diagnosis and pharmacogenetics
INVENTOR(S): Nevins, Joseph; West, Mike; Goldschmidt, Pascal
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 408 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003091391	A2	20031106	WO 2002-US38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2003091391	A2	20031106	WO 2002-XA38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2003091391	A2	20031106	WO 2002-XB38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002364707	A1	20031110	AU 2002-364707	20021112
EP 1578918	A2	20050928	EP 2002-807324	20021112
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				

PRIORITY APPLN. INFO.:	US 2002-374547P	P	20020423
	US 2002-420784P	P	20021024
	US 2002-421043P	P	20021025
	US 2002-424680P	P	20021108
	WO 2002-US38221	A	20021112

AB Genes whose expression is correlated with an determinant of an atherosclerotic phenotype are provided. Also provided are methods of using the subject atherosclerotic determinant genes in diagnosis and treatment methods, as well as drug screening methods. In addition, reagents and kits thereof that find use in practicing the subject methods are provided. Also provided are methods of determining whether a gene is correlated with a disease phenotype, where correlation is determined using a Bayesian anal.

L14 ANSWER 5 OF 8 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:204833 BIOSIS
DOCUMENT NUMBER: PREV200400205373
TITLE: The effect of Akt by antidepressants in the rat brain.
AUTHOR(S): Misonoo, A. [Reprint Author]; Kenichi, O. [Reprint Author]; Hsagawa, H. [Reprint Author]; Kiyofumi, T. [Reprint Author]; Kanai, S. [Reprint Author]; Tanaka, D. [Reprint Author]; Hisinuma, T. [Reprint Author]; Fujii, S. [Reprint Author]; Sasuga, Y. [Reprint Author]; Miyamoto, S. [Reprint Author]; Asakura, M. [Reprint Author]
CORPORATE SOURCE: Dept. Neuropsych, St. Marianna Univ. Sch. Med, Kawasaki, Japan

SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 849.15. http://sfn.scholarone.com. e-file.
Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Apr 2004
Last Updated on STN: 14 Apr 2004

AB Akt, also known as protein kinase B, is a protein kinase as a downstream kinase of phosphoinositide 3-kinase (PI3-K) and BDNF. Phoshporylation of residues Ser-473 and Thr-308 is required for Akt activity by PDK1 and PDK2, respectively. PRK2 inhibits the phosphorylation of Akt Ser-473 by PDK1. Key roles for Akt in cellular processes such as apotosis, neurotransmitters release and transcription are now well established.The phosphorylation of Akt Ser-473 and Thr-308 increased after 3 weeks Clomipramine and Fluvoxamine treatment by Immunoblot measurement. PDK1 and PDK1, Ser-241 phosphorylation also increased after treatment of antidepressants. But PI3-K and PRK2 were not changed by antidepressants.Akt is known to play a role in the releasing process for several neurotransmitters (5-HT and NE). It is important cellular mechanism for antidepressants that Akt activated by PDK.

L14 ANSWER 6 OF 8 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:167581 BIOSIS
DOCUMENT NUMBER: PREV200200167581
TITLE: Regulation of both PDK1 and the phosphorylation of PKC-zeta and -delta by a C-terminal PRK2 fragment.
AUTHOR(S): Hodgkinson, Conrad P.; Sale, Graham J. [Reprint author]
CORPORATE SOURCE: Division of Biochemistry and Molecular Biology, School of Biological Sciences, University of Southampton, Bassett Crescent East, Biomedical Sciences Building, Southampton, SO16 7PX, UK
G.J.Sale@soton.ac.uk
SOURCE: Biochemistry, (January 15, 2002) Vol. 41, No. 2, pp. 561-569. print.
CODEN: BICHAW. ISSN: 0006-2960.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Mar 2002
Last Updated on STN: 5 Mar 2002

AB The mechanism by which PDK1 regulates AGC kinases remains unclear. To further understand this process, we performed a yeast two-hybrid screen using PDK1 as bait. PKC-zeta, PKC-delta, and PRK2 were identified as interactors of PDK1. A combination of yeast two-hybrid binding assays and coprecipitation from mammalian cells was used to characterize the nature of the PDK1-PKC interaction. The presence of the PH domain of PDK1 inhibited the interaction of PDK1 with the PKCs. A contact region of PDK1 was mapped between residues 314 and 408. The interaction of PDK1 with the PKCs required the full-length PKC-zeta and -delta proteins apart from their C-terminal tails. PDK1 was able to phosphorylate full-length PKC-zeta and -delta but not PKC-zeta and -delta constructs containing the PDK1 phosphorylation site but lacking the C-terminal tails. A C-terminal PRK2 fragment, normally produced by caspase-3 cleavage during apoptosis, inhibited PDK1 autophosphorylation by >90%. The ability of PDK1 to phosphorylate PKC-zeta and -delta in vitro was also markedly inhibited by the PRK2 fragment. Additionally, generation of the PRK2 fragment in vivo inhibited by >90% the phosphorylation of endogenous PKC-zeta by PDK1. In conclusion, these results show that the C-terminal tail of PKC is a critical determinant for PKC-zeta and -delta phosphorylation by PDK1. Moreover, the C-terminal PRK2 fragment acts as a potent negative

regulator of PDK1 autophosphorylation and PDK1 kinase activity against PKC-zeta and -delta. As the C-terminal PRK2 fragment is naturally generated during apoptosis, this may provide a mechanism of restraining prosurvival signals during apoptosis.

L14 ANSWER 7 OF 8 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:386006 BIOSIS
DOCUMENT NUMBER: PREV199900386006
TITLE: Kinase phosphorylation: Keeping it all in the family.
AUTHOR(S): Peterson, Randall T. [Reprint author]; Schreiber, Stuart L. [Reprint author]
CORPORATE SOURCE: Departments of Chemistry and Chemical Biology and Molecular and Cellular Biology, Howard Hughes Medical Institute, Harvard University, Cambridge, MA, 02138, USA
SOURCE: Current Biology, (July 15, 1999) Vol. 9, No. 14, pp. R521-R524. print.
CODEN: CUBLE2. ISSN: 0960-9822.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Sep 1999
Last Updated on STN: 28 Sep 1999

AB The identification of PDK1 as a kinase that phosphorylates the AGC family of kinases led to a hunt for 'PDK2', a hypothetical regulated kinase(s) that would be required for full activation of the AGC kinases. Recent findings suggest that the elusive PDK2 may actually be a familiar kinase with an atypical associate.

L14 ANSWER 8 OF 8 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 1999244939 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10226025
TITLE: PDK1 acquires PDK2 activity in the presence of a synthetic peptide derived from the carboxyl terminus of PRK2.
AUTHOR: Balendran A; Casamayor A; Deak M; Paterson A; Gaffney P; Currie R; Downes C P; Alessi D R
CORPORATE SOURCE: MRC Protein Phosphorylation Unit, Department of Biochemistry, University of Dundee, Dundee DD1 5EH, UK.
SOURCE: Current biology : CB, (1999 Apr 22) Vol. 9, No. 8, pp. 393-404.
Journal code: 9107782. ISSN: 0960-9822.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 14 Jun 1999
Last Updated on STN: 20 Apr 2002
Entered Medline: 1 Jun 1999

AB BACKGROUND: Protein kinase B (PKB) is activated by phosphorylation of Thr308 and of Ser473. Thr308 is phosphorylated by the 3-phosphoinositide-dependent protein kinase-1 (PDK1) but the identity of the kinase that phosphorylates Ser473 (provisionally termed PDK2) is unknown. RESULTS: The kinase domain of PDK1 interacts with a region of protein kinase C-related kinase-2 (PRK2), termed the PDK1-interacting fragment (PIF). PIF is situated carboxy-terminal to the kinase domain of PRK2, and contains a consensus motif for phosphorylation by PDK2 similar to that found in PKBalpha, except that the residue equivalent to Ser473 is aspartic acid. Mutation of any of the conserved residues in the PDK2 motif of PIF prevented interaction of PIF with PDK1. Remarkably, interaction of PDK1 with PIF, or with a synthetic peptide encompassing the PDK2 consensus sequence of PIF, converted PDK1 from an enzyme that could phosphorylate only Thr308 of PKBalpha to one that phosphorylates both Thr308 and Ser473 of PKBalpha in a manner dependent on

phosphatidylinositol (3,4,5) trisphosphate (PtdIns(3,4,5)P3). Furthermore, the interaction of PIF with PDK1 converted the PDK1 from a form that is not directly activated by PtdIns(3,4,5)P3 to a form that is activated threefold by PtdIns(3,4,5)P3. We have partially purified a kinase from brain extract that phosphorylates Ser473 of PKBalpha in a PtdIns(3,4,5)P3-dependent manner and that is immunoprecipitated with PDK1 antibodies. CONCLUSIONS: PDK1 and PDK2 might be the same enzyme, the substrate specificity and activity of PDK1 being regulated through its interaction with another protein(s). PRK2 is a probable substrate for PDK1.

```
=> s PKB (w)activat?
L15        1023 PKB (W) ACTIVAT?

=> d his

     (FILE 'HOME' ENTERED AT 10:08:25 ON 28 JUL 2006)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
    LIFESCI' ENTERED AT 10:08:53 ON 28 JUL 2006
L1         67106 S PHOSPHOINOSITIDE
L2         19704 S L1 (2W) KINASE##
L3          2205 S PDK1
L4         20665 S L2 OR L3
L5           319 S PRK2
L6            60 S L4 AND L5
L7            27 DUP REM L6 (33 DUPLICATES REMOVED)
L8            12 S L5 AND PIF
L9             3 DUP REM L8 (9 DUPLICATES REMOVED)
L10          346 S PKC (W)RELATED
L11           43 S L5 AND L10
L12           31 DUP REM L11 (12 DUPLICATES REMOVED)
L13           18 S PDK2 AND L5
L14            8 DUP REM L13 (10 DUPLICATES REMOVED)
L15         1023 S PKB (W)ACTIVAT?

=> s l3 and l15
L16          72 L3 AND L15

=> dup rem l16
PROCESSING COMPLETED FOR L16
L17          19 DUP REM L16 (53 DUPLICATES REMOVED)

=> d 1-19 ibib ab

L17  ANSWER 1 OF 19     MEDLINE on STN                    DUPLICATE 1
ACCESSION NUMBER:   2005088955     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 15718470
TITLE:              Phosphorylation and regulation of Akt/PKB by the
                    rictor-mTOR complex.
AUTHOR:             Sarbassov D D; Guertin David A; Ali Siraj M; Sabatini David
                    M
CORPORATE SOURCE:   Whitehead Institute for Biomedical Research and Department
                    of Biology, Massachusetts Institute of Technology, Nine
                    Cambridge Center, Cambridge, MA 02142, USA.
CONTRACT NUMBER:    R01 AI47389 (NIAID)
SOURCE:             Science, (2005 Feb 18) Vol. 307, No. 5712, pp. 1098-101.
                    Journal code: 0404511. E-ISSN: 1095-9203.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200503
```

ENTRY DATE: Entered STN: 19 Feb 2005
Last Updated on STN: 3 Mar 2005
Entered Medline: 2 Mar 2005

AB Deregulation of Akt/protein kinase B (PKB) is implicated in the pathogenesis of cancer and diabetes. Akt/PKB activation requires the phosphorylation of Thr308 in the activation loop by the phosphoinositide-dependent kinase 1 (PDK1) and Ser473 within the carboxyl-terminal hydrophobic motif by an unknown kinase. We show that in Drosophila and human cells the target of rapamycin (TOR) kinase and its associated protein rictor are necessary for Ser473 phosphorylation and that a reduction in rictor or mammalian TOR (mTOR) expression inhibited an Akt/PKB effector. The rictor-mTOR complex directly phosphorylated Akt/PKB on Ser473 in vitro and facilitated Thr308 phosphorylation by PDK1 . Rictor-mTOR may serve as a drug target in tumors that have lost the expression of PTEN, a tumor suppressor that opposes Akt/PKB activation.

L17 ANSWER 2 OF 19 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2005265572 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15909115
TITLE: Sustained Akt/PKB activation and transient attenuation of c-jun N-terminal kinase in the inhibition of apoptosis by IGF-1 in vascular smooth muscle cells.
AUTHOR: Allen R T; Krueger K D; Dhume A; Agrawal D K
CORPORATE SOURCE: Departments of Medical Microbiology and Immunology, Creighton University School of Medicine, Omaha, NE 68178, USA.
CONTRACT NUMBER: R01HL070885 (NHLBI)
R01HL073349 (NHLBI)
SOURCE: Apoptosis : an international journal on programmed cell death, (2005 May) Vol. 10, No. 3, pp. 525-35.
Journal code: 9712129. ISSN: 1360-8185.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200509
ENTRY DATE: Entered STN: 24 May 2005
Last Updated on STN: 28 Sep 2005
Entered Medline: 27 Sep 2005

AB Characteristics of hVSMC apoptosis and its inhibition by insulin-like growth factor-1 (IGF-1) remain unclear. Also unclear is whether a balance in hVSMCs exists whereby c-Jun N-terminal stress kinases (JNK) promote apoptosis while extracellular signal-regulated (ERK1/2) MAP kinases inhibit cell death. In this study, we examined the involvement of Akt/PKB and its upstream kinase, PDK1 and whether JNK activation correlated with human and rat VSMC apoptosis induced by staurosporine and by c-myc, respectively. We observed a strong, sustained JNK activation (and c-Jun phosphorylation), which correlated with VSMC apoptosis. IGF-1 (13.3 nM), during apoptosis inhibition, transiently inhibited JNK activity at 1 h in a phosphatidylinositol 3-kinase (PI3-K)- and MEK-ERK-dependent manner, as wortmannin (100 nM) or PD98059 (30 muM) partially attenuated the IGF-1 effect. PKC down-regulation had no effect on JNK inhibition by IGF-1. While IGF-1 alone produced a strong phosphorylation of Akt/PKB in hVSMCs up to 6 h, it was notably stronger and more sustained during ratmyc and hVSMCs apoptosis inhibition. Further, whereas transient expression of phosphorylated Akt protected VSMCs from apoptosis by nearly 50%, expression of dominant interfering alleles of Akt or PDK1 strongly inhibited IGF-1-mediated VSMC survival. These results demonstrate for the first time that transient inhibition of a pro-apoptotic stimulus in VSMCs may be sufficient to inhibit a programmed cell death and that sustained anti-apoptotic signals (Akt) elicited by IGF-1 are augmented during a death stimulus. Furthermore, PI3-K and

ERK-MAPK pathways may cooperate to protect VSMCs from cell death.

L17 ANSWER 3 OF 19 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2004393025 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15297428
TITLE: In vitro combination treatment with perifosine and UCN-01 demonstrates synergism against prostate (PC-3) and lung (A549) epithelial adenocarcinoma cell lines.
AUTHOR: Dasmahapatra Girija P; Didolkar Parijat; Alley Michael C; Ghosh Somiranjan; Sausville Edward A; Roy Krishnendu K
CORPORATE SOURCE: Clinical Trials Unit, Developmental Therapeutics Program, National Cancer Institute, Bethesda, Maryland 20892, USA.
SOURCE: Clinical cancer research : an official journal of the American Association for Cancer Research, (2004 Aug 1) Vol. 10, No. 15, pp. 5242-52.
Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200503
ENTRY DATE: Entered STN: 7 Aug 2004
Last Updated on STN: 8 Mar 2005
Entered Medline: 7 Mar 2005

AB PURPOSE: Antineoplastic agents often achieve antitumor activity at the expense of close to unacceptable toxicity. One potential avenue to improve therapeutic index might combine agents targeting distinct components of the same growth regulatory pathway. This might lead to more complete modulation of the target pathway at concentrations lower than those associated with limiting adventitious toxicities from either agent alone. The protein kinase antagonist UCN-01 is currently used in Phase I/II trials and has recently been demonstrated to inhibit potently PDK1. We have recently documented that the alkylphospholipid perifosine potently also inhibits Akt kinase (PKB) activation by interfering with membrane localization of Akt. This leads to the hypothesis that these two agents might act synergistically through distinct mechanisms in the PI3K/Akt proliferation and survival-related signaling pathway. EXPERIMENTAL DESIGN: The synergistic effects of UCN-01 and perifosine, on two cell lines (A-549 and PC-3), were examined using various long-term in vitro assays for cell growth, cell cycle distribution, clonogenicity, survival morphology, and apoptosis. Along with Western blotting experiments were performed to determine whether this synergistic combination of two drugs has significant effect on their downstream targets and on biochemical markers of apoptosis. RESULTS: After 72 h, perifosine at concentrations of 1.5 and 10 microM UCN-01 at 40 and 250 nM did not significantly affect the growth of PC-3 and A459 cells, respectively. However, in combination at the same respective individual concentrations (1.5 microM and 40 nM of perifosine and UCN-01, respectively, in PC-3 cells and 10 microM perifosine and 0.25 microM UCN-01 in the somewhat more resistant A549 cells), virtually complete growth inhibition of both the cell lines resulted. Supra-additive inhibition of growth was also demonstrated in independent clonogenic assays. Mechanistic studies in cell culture models suggest enhanced depletion of the S-phase population in cells treated by the combination. This correlated with enhanced inactivation of Akt along with activation of caspases 3 and 9 and poly(ADP-ribose) polymerase cleavage. Evidence of synergy was formally demonstrated and occurred across a wide range of drug concentrations and was largely independent of the order or sequence of drug addition. CONCLUSIONS: As the concentrations of UCN-01 and perifosine causing synergistic inhibition of cell growth are clinically achievable without prominent toxicity, these data support the development of clinical studies with this combination.

L17 ANSWER 4 OF 19 MEDLINE on STN DUPLICATE 4

ACCESSION NUMBER: 2003197430 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12594228
TITLE: Phosphoinositide 3-kinase-mediated reduction of insulin receptor substrate-1/2 protein expression via different mechanisms contributes to the insulin-induced desensitization of its signaling pathways in L6 muscle cells.
AUTHOR: Pirola Luciano; Bonnafous Stephanie; Johnston Anne M; Chaussade Claire; Portis Fiorella; Van Obberghen Emmanuel
CORPORATE SOURCE: INSERM U145, IFR50, Faculte de Medecine, 06107 Nice Cedex 2, France.
SOURCE: The Journal of biological chemistry, (2003 May 2) Vol. 278, No. 18, pp. 15641-51. Electronic Publication: 2003-02-18. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 29 Apr 2003
Last Updated on STN: 18 Jun 2003
Entered Medline: 17 Jun 2003

AB Impaired glucose tolerance precedes type 2 diabetes and is characterized by hyperinsulinemia, which develops to balance peripheral insulin resistance. To gain insight into the deleterious effects of hyperinsulinemia on skeletal muscle, we studied the consequences of prolonged insulin treatment of L6 myoblasts on insulin-dependent signaling pathways. A 24-h long insulin treatment desensitized the phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB) and p42/p44 MAPK pathways toward a second stimulation with insulin or insulin-like growth factor-1 and led to decreased insulin-induced glucose uptake. Desensitization was correlated to a reduction in insulin receptor substrate (IRS)-1 and IRS-2 protein levels, which was reversed by the PI3K inhibitor LY294002. Co-treatment of cells with insulin and LY294002, while reducing total IRS-1 phosphorylation, increased its phosphotyrosine content, enhancing IRS-1/PI3K association. PDK1, mTOR, and MAPK inhibitors did not block insulin-induced reduction of IRS-1, suggesting that the PI3K serine-kinase activity causes IRS-1 serine phosphorylation and its commitment to proteasomal degradation. Contrarily, insulin-induced IRS-2 down-regulation occurred via a PI3K/mTOR pathway. Suppression of IRS-1/2 down-regulation by LY294002 rescued the responsiveness of PKB and MAPK toward acute insulin stimulation. Conversely, adenoviral-driven expression of constitutively active PI3K induced an insulin-independent reduction in IRS-1/2 protein levels. IRS-2 appears to be the chief molecule responsible for MAPK and PKB activation by insulin, as knockdown of IRS-2 (but not IRS-1) by RNA interference severely impaired activation of both kinases. In summary, (i) PI3K mediates insulin-induced reduction of IRS-1 by phosphorylating it while a PI3K/mTOR pathway controls insulin-induced reduction of IRS-2, (ii) in L6 cells, IRS-2 is the major adapter molecule linking the insulin receptor to activation of PKB and MAPK, (iii) the mechanism of IRS-1/2 down-regulation is different in L6 cells compared with 3T3-L1 adipocytes. In conclusion, the reduction in IRS proteins via different PI3K-mediated mechanisms contributes to the development of an insulin-resistant state in L6 myoblasts.

L17 ANSWER 5 OF 19 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2002204816 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11825911
TITLE: Protein kinase B is regulated in platelets by the collagen receptor glycoprotein VI.
AUTHOR: Barry Fiona A; Gibbins Jonathan M
CORPORATE SOURCE: School of Animal & Microbial Sciences, University of Reading, Whiteknights, Reading RG6 6AJ, United Kingdom.

SOURCE: The Journal of biological chemistry, (2002 Apr 12) Vol. 277, No. 15, pp. 12874-8. Electronic Publication: 2002-02-01.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 9 Apr 2002
Last Updated on STN: 5 Jan 2003
Entered Medline: 16 May 2002

AB Phosphoinositide 3-kinase (PI3K) is a critical component of the signaling pathways that control the activation of platelets. Here we have examined the regulation of protein kinase B (PKB), a downstream effector of PI3K, by the platelet collagen receptor glycoprotein (GP) VI and thrombin receptors. Stimulation of platelets with collagen or convulxin (a selective GPVI agonist) resulted in PI3K-dependent, and aggregation independent, Ser(473) and Thr(308) phosphorylation of PKBalpha, which results in PKB activation. This was accompanied by translocation of PKB to cell membranes. The phosphoinositide-dependent kinase PDK1 is known to phosphorylate PKBalpha on Thr(308), although the identity of the kinase responsible for Ser(473) phosphorylation is less clear. One candidate that has been implicated as being responsible for Ser(473) phosphorylation, either directly or indirectly, is the integrin-linked kinase (ILK). In this study we have examined the interactions of PKB, PDK1, and ILK in resting and stimulated platelets. We demonstrate that in platelets PKB is physically associated with PDK1 and ILK. Furthermore, the association of PDK1 and ILK increases upon platelet stimulation. It would therefore appear that formation of a tertiary complex between PDK1 , ILK, and PKB may be necessary for phosphorylation of PKB. These observations indicate that PKB participates in cell signaling downstream of the platelet collagen receptor GPVI. The role of PKB in collagen- and thrombin-stimulated platelets remains to be determined.

L17 ANSWER 6 OF 19 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2002413471 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12167717
TITLE: Multiple phosphoinositide 3-kinase-dependent steps in activation of protein kinase B.
AUTHOR: Scheid Michael P; Marignani Paola A; Woodgett James R
CORPORATE SOURCE: Department of Experimental Therapeutics, University Health Network. Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada.
SOURCE: Molecular and cellular biology, (2002 Sep) Vol. 22, No. 17, pp. 6247-60.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 9 Aug 2002
Last Updated on STN: 10 Sep 2002
Entered Medline: 9 Sep 2002

AB The protein kinase B (PKB)/Akt family of serine kinases is rapidly activated following agonist-induced stimulation of phosphoinositide 3-kinase (PI3K). To probe the molecular events important for the activation process, we employed two distinct models of posttranslational inducible activation and membrane recruitment. PKB induction requires phosphorylation of two critical residues, threonine 308 in the activation loop and serine 473 near the carboxyl terminus. Membrane localization of PKB was found to be a primary determinant of serine 473 phosphorylation.

PI3K activity was equally important for promoting phosphorylation of serine 473, but this was separable from membrane localization. PDK1 phosphorylation of threonine 308 was primarily dependent upon prior serine 473 phosphorylation and, to a lesser extent, localization to the plasma membrane. Mutation of serine 473 to alanine or aspartic acid modulated the degree of threonine 308 phosphorylation in both models, while a point mutation in the substrate-binding region of PDK1 (L155E) rendered PDK1 incapable of phosphorylating PKB. Together, these results suggest a mechanism in which 3' phosphoinositide lipid-dependent translocation of PKB to the plasma membrane promotes serine 473 phosphorylation, which is, in turn, necessary for PDK1 -mediated phosphorylation of threonine 308 and, consequentially, full PKB activation.

L17 ANSWER 7 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:419947 BIOSIS
DOCUMENT NUMBER: PREV200200419947
TITLE: Ras signaling in the control of cell survival.
AUTHOR(S): Downward, Julian [Reprint author]
CORPORATE SOURCE: Imperial Cancer Research Fund, London, UK
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2002) Vol. 43, pp. 1162. print. Meeting Info.: 93rd Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 06-10, 2002. ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Aug 2002
Last Updated on STN: 7 Aug 2002

L17 ANSWER 8 OF 19 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2001532354 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11481324
TITLE: Insulin receptor substrate-2 phosphorylation is necessary for protein kinase C zeta activation by insulin in L6hIR cells.
AUTHOR: Oriente F; Formisano P; Miele C; Fiory F; Maitan M A; Vigliotta G; Trencia A; Santopietro S; Caruso M; Van Obberghen E; Beguinot F
CORPORATE SOURCE: Dipartimento di Biologia e Patologia Cellulare e Molecolare, Federico II University of Naples, 80131 Italy.
SOURCE: The Journal of biological chemistry, (2001 Oct 5) Vol. 276, No. 40, pp. 37109-19. Electronic Publication: 2001-07-31. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 2 Oct 2001
Last Updated on STN: 5 Jan 2003
Entered Medline: 4 Dec 2001

AB We have investigated glycogen synthase (GS) activation in L6hIR cells expressing a peptide corresponding to the kinase regulatory loop binding domain of insulin receptor substrate-2 (IRS-2) (KRLB). In several clones of these cells (B2, F4), insulin-dependent binding of the KRLB to insulin receptors was accompanied by a block of IRS-2, but not IRS-1, phosphorylation, and insulin receptor binding. GS activation by insulin was also inhibited by >70% in these cells ($p < 0.001$). The impairment of GS activation was paralleled by a similarly sized inhibition of glycogen synthase kinase 3 alpha (GSK3 alpha) and GSK3 beta inactivation by insulin with no change in protein phosphatase 1 activity. PDK1 (a

phosphatidylinositol trisphosphate-dependent kinase) and Akt/protein kinase B (PKB) activation by insulin showed no difference in B2, F4, and in control L6hIR cells. At variance, insulin did not activate PKC zeta in B2 and F4 cells. In L6hIR, inhibition of PKC zeta activity by either a PKC zeta antisense or a dominant negative mutant also reduced by 75% insulin inactivation of GSK3 alpha and -beta ($p < 0.001$) and insulin stimulation of GS ($p < 0.002$), similar to Akt/PKB inhibition. In L6hIR, insulin induced protein kinase C zeta (PKC zeta) co-precipitation with GSK3 alpha and beta. PKC zeta also phosphorylated GSK3 alpha and -beta. Alone, these events did not significantly affect GSK3 alpha and -beta activities. Inhibition of PKC zeta activity, however, reduced Akt/PKB phosphorylation of the key serine sites on GSK3 alpha and -beta by >80% ($p < 0.001$) and prevented full GSK3 inactivation by insulin. Thus, IRS-2, not IRS-1, signals insulin activation of GS in the L6hIR skeletal muscle cells. In these cells, insulin inhibition of GSK3 alpha and -beta requires dual phosphorylation by both Akt/PKB and PKC zeta.

L17 ANSWER 9 OF 19 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2001389026 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11373274
TITLE: Insulin-stimulated protein kinase B phosphorylation on Ser-473 is independent of its activity and occurs through a staurosporine-insensitive kinase.
AUTHOR: Hill M M; Andjelkovic M; Brazil D P; Ferrari S; Fabbro D; Hemmings B A
CORPORATE SOURCE: Friedrich Miescher Institute, Maulbeerstrasse 66, CH-4058 Basel, Switzerland.
SOURCE: The Journal of biological chemistry, (2001 Jul 13) Vol. 276, No. 28, pp. 25643-6. Electronic Publication: 2001-05-23.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20 Aug 2001
Last Updated on STN: 5 Jan 2003
Entered Medline: 16 Aug 2001

AB Full activation of protein kinase B (PKB, also called Akt) requires phosphorylation on two regulatory sites, Thr-308 in the activation loop and Ser-473 in the hydrophobic C-terminal regulatory domain (numbering for PKB alpha/Akt-1). Although 3'-phosphoinositide-dependent protein kinase 1 (PDK1) has now been identified as the Thr-308 kinase, the mechanism of the Ser-473 phosphorylation remains controversial. As a step to further characterize the Ser-473 kinase, we examined the effects of a range of protein kinase inhibitors on the activation and phosphorylation of PKB. We found that staurosporine, a broad-specificity kinase inhibitor and inducer of cell apoptosis, attenuated PKB activation exclusively through the inhibition of Thr-308 phosphorylation, with Ser-473 phosphorylation unaffected. The increase in Thr-308 phosphorylation because of overexpression of PDK1 was also inhibited by staurosporine. We further show that staurosporine (CGP 39360) potently inhibited PDK1 activity in vitro with an IC(50) of approximately 0.22 microm. These data indicate that agonist-induced phosphorylation of Ser-473 of PKB is independent of PDK1 or PKB activity and occurs through a distinct Ser-473 kinase that is not inhibited by staurosporine. Moreover, our results suggest that inhibition of PKB signaling is involved in the proapoptotic action of staurosporine.

L17 ANSWER 10 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:557824 BIOSIS

DOCUMENT NUMBER: PREV200100557824
TITLE: 5-HT secretion induced by a G-protein coupled receptor (CaR) for extracellular Ca2+ ((Ca2+)e).
AUTHOR(S): Tamir, H. [Reprint author]; Liu, K. P. [Reprint author]; Russo, A. F.; Hsiung, S. C. [Reprint author]; Adlersberg, M. [Reprint author]; Gershon, M. D.
CORPORATE SOURCE: Dept Neuroscience, NY State Psychiatric Inst, New York, NY, USA
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 1841. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001.
ISSN: 0190-5295.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Dec 2001
Last Updated on STN: 25 Feb 2002

AB The CaR was discovered in cells that respond to changes in (Ca2+)e but is also expressed in neurons. 5-HT secretion by parafollicular (PF) cells in response to uparw(Ca2+)e and secretory vesicle acidification are CaR-mediated; therefore, these neural crest-derived cells are useful models for CaR studies. We have proposed two transduction pathways for CaR-stimulated 5-HT secretion. One, initiated by Galphai, involves phosphatidylinositol phospholipase C, uparw(Ca2+)I and activation of PKCgamma. The other, initiated by Gbeta/gamma, involves phosphatidylinositol 3'-kinase (PI3'-kinase), which activates PKCzeta and or AKT/PKB. We infected PF cells with adenoviral vectors containing constructs encoding dominant-negative mutant forms of the CaR, PI3'-kinase, and PKCzeta. Each of these constructs strongly attenuated (55-80%) the uparw(Ca2+)e-induced secretion of 5-HT but the vector alone did not. The down-stream effector for PI3'-kinase in PF cells is 3'-phosphoinositide-dependent protein kinase-1 (PDK1), which activates effectors such as PKCzeta and AKT/PKB by their phosphorylation. Following stimulation, we detected the phosphorylated form of PKCzeta. PKCzeta phosphorylation was attenuated by LY-294002, a PI3'-kinase inhibitor. Infection of cells with constructs encoding a constitutively active AKT (in an adenoviral vector) induced constitutive 5-HT secretion, which was not affected by inhibiting PI3'-kinase. We conclude that CaR-mediated 5-HT secretion is transduced, at least in part, via PKCzeta PI3'-kinase and AKT/PKB.

L17 ANSWER 11 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:446885 BIOSIS
DOCUMENT NUMBER: PREV200100446885
TITLE: Evidence that Src family non-receptor tyrosine kinases relay information from both IGF-I and insulin receptors to the 70 kDa S6 ribosomal protein kinase.
AUTHOR(S): Shah, O. Jameel [Reprint author]; Kimball, Scot R. [Reprint author]; Jefferson, Leonard S. [Reprint author]
CORPORATE SOURCE: Hershey, PA, USA
SOURCE: Diabetes, (June, 2001) Vol. 50, No. Supplement 2, pp. A297. print.
Meeting Info.: 61st Scientific Sessions of the American Diabetes Association. Philadelphia, Pennsylvania, USA. June 22-26, 2001. American Diabetes Association.
CODEN: DIAEAZ. ISSN: 0012-1797.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Sep 2001

Last Updated on STN: 22 Feb 2002

L17 ANSWER 12 OF 19 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2000496001 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10874027
TITLE: Dual regulation of platelet protein kinase B.
AUTHOR: Kroner C; Eybrechts K; Akkerman J W
CORPORATE SOURCE: Department of Haematology, Laboratory for Thrombosis and Haemostasis, University Medical Center Utrecht and Institute for Biomembranes, Utrecht University, 3584 CX Utrecht, The Netherlands.. ckroner@lab.azu.nl
SOURCE: The Journal of biological chemistry, (2000 Sep 8) Vol. 275, No. 36, pp. 27790-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 27 Oct 2000
Last Updated on STN: 27 Oct 2000
Entered Medline: 13 Oct 2000

AB Protein kinase B (PKB) is a serine/threonine kinase that is activated by growth hormones and implicated in prevention of apoptosis, glycogen metabolism, and glucose uptake. A key enzyme in PKB activation is phosphatidylinositide 3-kinase (PI-3K), which triggers the dual phosphorylation of PKB by phosphatidylinositol-dependent kinases (PDKs). Here we report that the major PKB subtype in platelets is PKBalpha, which is activated by phosphorylation of Thr(308) and Ser(473) and has a constitutively phosphorylated Thr(450) that does not contribute to PKB activation. alpha-Thrombin and thrombopoietin activate PKBalpha via PI-3K and trigger the concurrent phosphorylation of Thr(308) (via PDK1) and Ser(473) (via a not yet identified PDK2). In addition, alpha-thrombin activates a PI-3K-independent pathway involving phospholipase Cbeta and calcium-dependent protein kinase C subtypes (PKCalpha/beta). This route is specific for phosphorylation of Ser(473) and can be initiated by direct PKC activation with phorbol ester or purified active PKC catalytic fragment in platelet lysate. Different degrees of Ser(473) and Thr(308) phosphorylation correlate with different degrees of enzyme activity. These data reveal a PI-3K-independent PKB activation in which PKCalpha/beta regulates the phosphorylation of Ser(473) in PKBalpha. The independent control of the two phosphorylation sites may contribute to fine regulation of PKBalpha activity.

L17 ANSWER 13 OF 19 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2000388538 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10891507
TITLE: Effect of phosphoinositide-dependent kinase 1 on protein kinase B translocation and its subsequent activation.
AUTHOR: Filippa N; Sable C L; Hemmings B A; Van Obberghen E
CORPORATE SOURCE: INSERM U145, IFR 50, Faculte de Medecine, 06107 Nice Cedex 2, France.
SOURCE: Molecular and cellular biology, (2000 Aug) Vol. 20, No. 15, pp. 5712-21.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 18 Aug 2000
Last Updated on STN: 20 Apr 2002
Entered Medline: 10 Aug 2000

AB In this report we investigated the function of phosphoinositide-dependent protein kinase 1 (PDK1) in protein kinase B (PKB) activation and translocation to the cell surface. Wild-type and PDK1 mutants were transfected into HeLa cells, and their subcellular localization was analyzed. PDK1 was found to translocate to the plasma membrane in response to insulin, and this process did not require a functional catalytic activity, since a catalytically inactive kinase mutant (Kd) of PDK1 was capable of translocating. The PDK1 presence at the cell surface was shown to be linked to phospholipids and therefore to serum-dependent phosphatidylinositol 3-kinase activity. Using confocal microscopy in HeLa cells we found that PDK1 colocalizes with PKB at the plasma membrane. Further, after cotransfection of PKB and a PDK1 mutant (Mut) unable to translocate to the plasma membrane, PKB was prevented from moving to the cell periphery after insulin stimulation. In response to insulin, a PKB mutant with its PH domain deleted (DeltaPH-PKB) retained the ability to translocate to the plasma membrane when coexpressed with PDK1. Finally, we found that DeltaPH-PKB was highly active independent of insulin stimulation when cotransfected with PDK1 mutants defective in their PH domain. These findings suggest that PDK1 brings PKB to the plasma membrane upon exposure of cells to insulin and that the PH domain of PDK1 acts as a negative regulator of its enzyme activity.

L17 ANSWER 14 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2000:179833 BIOSIS
DOCUMENT NUMBER: PREV200000179833
TITLE: The PI3K-PDK1 connection: More than just a road to PKB.
AUTHOR(S): Vanhaesebroeck, Bart [Reprint author]; Alessi, Dario R.
CORPORATE SOURCE: Cell Signalling Group, Ludwig Institute for Cancer Research, 91 Riding House Street, London, W1P 8BT, UK
SOURCE: Biochemical Journal, (March 15, 2000) Vol. 346, No. 3, pp. 561-576. print.
ISSN: 0264-6021.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 11 May 2000
Last Updated on STN: 4 Jan 2002

AB Phosphoinositide 3-kinases (PI3Ks) generate specific inositol lipids that have been implicated in the regulation of cell growth, proliferation, survival, differentiation and cytoskeletal changes. One of the best characterized targets of PI3K lipid products is the protein kinase Akt or protein kinase B (PKB). In quiescent cells, PKB resides in the cytosol in a low-activity conformation. Upon cellular stimulation, PKB is activated through recruitment to cellular membranes by PI3K lipid products and phosphorylation by 3'-phosphoinositide-dependent kinase-1 (PDK1). Here we review the mechanism by which PKB is activated and the downstream actions of this multifunctional kinase. We also discuss the evidence that PDK1 may be involved in the activation of protein kinases other than PKB, the mechanisms by which this activity of PDK1 could be regulated and the possibility that some of the currently postulated PKB substrates targets might in fact be phosphorylated by PDK1-regulated kinases other than PKB.

L17 ANSWER 15 OF 19 MEDLINE on STN DUPLICATE 11

ACCESSION NUMBER: 1999303798 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10373555
TITLE: Domain swapping used to investigate the mechanism of protein kinase B regulation by 3-phosphoinositide-dependent protein kinase 1 and Ser473 kinase.
AUTHOR: Andjelkovic M; Maira S M; Cron P; Parker P J; Hemmings B A

CORPORATE SOURCE: Friedrich Miescher-Institut, CH-4058 Basel, Switzerland.
SOURCE: Molecular and cellular biology, (1999 Jul) Vol. 19, No. 7, pp. 5061-72.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 30 Jul 1999
Last Updated on STN: 20 Apr 2002
Entered Medline: 22 Jul 1999

AB Protein kinase B (PKB or Akt), a downstream effector of phosphoinositide 3-kinase (PI 3-kinase), has been implicated in insulin signaling and cell survival. PKB is regulated by phosphorylation on Thr308 by 3-phosphoinositide-dependent protein kinase 1 (PDK1) and on Ser473 by an unidentified kinase. We have used chimeric molecules of PKB to define different steps in the activation mechanism. A chimera which allows inducible membrane translocation by lipid second messengers that activate in vivo protein kinase C and not PKB was created. Following membrane attachment, the PKB fusion protein was rapidly activated and phosphorylated at the two key regulatory sites, Ser473 and Thr308, in the absence of further cell stimulation. This finding indicated that both PDK1 and the Ser473 kinase may be localized at the membrane of unstimulated cells, which was confirmed for PDK1 by immunofluorescence studies. Significantly, PI 3-kinase inhibitors prevent the phosphorylation of both regulatory sites of the membrane-targeted PKB chimera. Furthermore, we show that PKB activated at the membrane was rapidly dephosphorylated following inhibition of PI 3-kinase, with Ser473 being a better substrate for protein phosphatase. Overall, the results demonstrate that PKB is stringently regulated by signaling pathways that control both phosphorylation/activation and dephosphorylation/inactivation of this pivotal protein kinase.

L17 ANSWER 16 OF 19 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:401775 HCAPLUS
DOCUMENT NUMBER: 131:42353
TITLE: PH domain and phosphoinositides. Regulation of Akt/PKB
AUTHOR(S): Ogawa, Wataru; Kasuga, Masato
CORPORATE SOURCE: Sch. Med., Kobe Univ., Japan
SOURCE: Jikken Igaku (1999), 17(10), 1190-1194
CODEN: JIIGEF; ISSN: 0288-5514
PUBLISHER: Yodosha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review with 23 refs., on the structure and functions of Akt/PKB , activation mechanism of Akt/PKB by phosphoinositides binding and phosphorylation, translocation pf Akt/PKB to plasma membrane, role of PH domain, activation of Akt/PKB by PI3-kinase-PDK1 system, and interaction between Akt/PKB and protein kinase C.

L17 ANSWER 17 OF 19 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 1999175477 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10074427
TITLE: Functional counterparts of mammalian protein kinases PDK1 and SGK in budding yeast.
AUTHOR: Casamayor A; Torrance P D; Kobayashi T; Thorner J; Alessi D R
CORPORATE SOURCE: MRC Protein Phosphorylation Unit Department of Biochemistry University of Dundee Dundee DD1 5EH Scotland UK.
CONTRACT NUMBER: GM21841 (NIGMS)
SOURCE: Current biology : CB, (1999 Feb 25) Vol. 9, No. 4, pp. 186-97.
Journal code: 9107782. ISSN: 0960-9822.

PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 4 May 1999
Last Updated on STN: 20 Apr 2002
Entered Medline: 22 Apr 1999

AB BACKGROUND: In animal cells, recruitment of phosphatidylinositol 3-kinase by growth factor receptors generates 3-phosphoinositides, which stimulate 3-phosphoinositide-dependent protein kinase-1 (PDK1). Activated PDK1 then phosphorylates and activates downstream protein kinases, including protein kinase B (PKB)/c-Akt, p70 S6 kinase, PKC isoforms, and serum- and glucocorticoid-inducible kinase (SGK), thereby eliciting physiological responses. RESULTS: We found that two previously uncharacterised genes of Saccharomyces cerevisiae, which we term PKH1 and PKH2, encode protein kinases with catalytic domains closely resembling those of human and Drosophila PDK1. Both Pkh1 and Pkh2 were essential for cell viability. Expression of human PDK1 in otherwise inviable pkh1Delta pkh2Delta cells permitted growth. In addition, the yeast YPK1 and YKR2 genes were found to encode protein kinases each with a catalytic domain closely resembling that of SGK; both Ypk1 and Ykr2 were also essential for viability. Otherwise inviable ypk1Delta ykr2Delta cells were fully rescued by expression of rat SGK, but not mouse PKB or rat p70 S6 kinase. Purified Pkh1 activated mammalian SGK and PKBalpha in vitro by phosphorylating the same residue as PDK1 . Pkh1 activated purified Ypk1 by phosphorylating the equivalent residue (Thr504) and was required for maximal Ypk1 phosphorylation in vivo. Unlike PKB, activation of Ypk1 and SGK by Pkh1 did not require phosphatidylinositol 3,4,5-trisphosphate, consistent with the absence of pleckstrin homology domains in these proteins. The phosphorylation consensus sequence for Ypk1 was similar to that for PKBalpha and SGK. CONCLUSIONS: Pkh1 and Pkh2 function similarly to PDK1, and Ypk1 and Ykr2 to SGK. As in animal cells, these two groups of yeast kinases constitute two tiers of a signalling cascade required for yeast cell growth.

L17 ANSWER 18 OF 19 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 1999171146 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10071752
TITLE: Regulation of protein kinase B.
AUTHOR: Meier R; Hemmings B A
CORPORATE SOURCE: Friedrich Miescher Institute, Basel, Switzerland.
SOURCE: Journal of receptor and signal transduction research, (1999 Jan-Jul) Vol. 19, No. 1-4, pp. 121-8. Ref: 29
Journal code: 9509432. ISSN: 1079-9893.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 28 Jun 1999
Last Updated on STN: 28 Jun 1999
Entered Medline: 15 Jun 1999

AB Protein kinase B (PKB) is a member of the second-messenger regulated subfamily of protein kinases implicated in signalling downstream of growth factor and insulin receptor tyrosine kinases and phosphatidylinositol 3-kinase (PI 3-kinase). PKB is activated by phosphorylation in response to mitogens and survival factors. Membrane recruitment driven by lipid second-messengers derived from PI 3-kinase leads to PKB phosphorylation and activation by upstream kinases (PDK1 and an as yet identified protein kinase). Prolonged stimulation with growth factors results in nuclear translocation, providing evidence that PKB

activation at the plasma membrane precedes its nuclear translocation and supporting a role for PKB in signalling from receptor tyrosine kinases to the nucleus.

L17 ANSWER 19 OF 19 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:373423 HCAPLUS
DOCUMENT NUMBER: 129:120493
TITLE: Translocation of PDK-1 to the plasma membrane is important in allowing PDK-1 to activate protein kinase B
AUTHOR(S): Anderson, Karen E.; Coadwell, John; Stephens, Len R.; Hawkins, Phillip T.
CORPORATE SOURCE: Inositide Lab., Dep. Signalling, The Babraham Inst., Babraham, Cambridge, CB2 4AT, UK
SOURCE: Current Biology (1998), 8(12), 684-691
CODEN: CUBLE2; ISSN: 0960-9822
PUBLISHER: Current Biology Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Protein kinase B (PKB) is involved in the regulation of apoptosis, protein synthesis, and glycogen metabolism in mammalian cells. Phosphoinositide-dependent protein kinase (PDK-1) activates PKB in a manner dependent on phosphatidylinositol 3,4,5-trisphosphate (PtdIns(3,4,5)P3), which is also needed for the translocation of PKB to the plasma membrane. It has been proposed that the amount of PKB activated is determined exclusively as a result of its translocation, and that a constitutively active pool of membrane-associated PDK-1 simply phosphorylates all the PKB made available. Here, the authors investigated the effects of membrane localization of PDK-1 on PKB activation. It was found that ectopically expressed PDK-1 translocated to the plasma membrane in response to platelet-derived growth factor (PDGF) and translocation was sensitive to wortmannin, an inhibitor of phosphoinositide 3-kinase. Translocation of PDK-1 also occurred upon its co-expression with constitutively active phosphoinositide 3-kinase, but not with an inactive form. Overexpression of PDK-1 enhanced the ability of PDGF to activate PKB. PDK-1 disrupted in the pleckstrin homol. (PH) domain which did not translocate to the membrane did not increase PKB activity in response to PDGF, whereas membrane-targeted PDK-1 activated PKB to the extent that it could not be activated further by PDGF. Thus, in response to PDGF, the binding of PtdIns(3,4,5)P3 and/or PtdIns(3,4)P2 to the PH domain of PDK-1 causes its translocation to the plasma membrane where it co-localizes with PKB, significantly contributing to the scale of PKB activation.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 10:08:25 ON 28 JUL 2006)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 10:08:53 ON 28 JUL 2006

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L1      67106 S PHOSPHOINOSITIDE
L2      19704 S L1 (2W) KINASE##
L3       2205 S PDK1
L4      20665 S L2 OR L3
L5        319 S PRK2
L6         60 S L4 AND L5
L7         27 DUP REM L6 (33 DUPLICATES REMOVED)
L8         12 S L5 AND PIF
L9          3 DUP REM L8 (9 DUPLICATES REMOVED)
L10       346 S PKC (W)RELATED
L11        43 S L5 AND L10
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L12          31 DUP REM L11 (12 DUPLICATES REMOVED)
L13          18 S PDK2 AND L5
L14           8 DUP REM L13 (10 DUPLICATES REMOVED)
L15        1023 S PKB (W)ACTIVAT?
L16          72 S L3 AND L15
L17          19 DUP REM L16 (53 DUPLICATES REMOVED)

=> s l5 and l15
L18           0 L5 AND L15

=> s l4 and l15
L19         248 L4 AND L15

=> s ser473
L20        1092 SER473

=> s l19 and l20
L21          43 L19 AND L20

=> dup rem l21
PROCESSING COMPLETED FOR L21
L22          15 DUP REM L21 (28 DUPLICATES REMOVED)

=> d 1-15 ibib ab

L22  ANSWER 1 OF 15  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2006:63780  HCAPLUS
DOCUMENT NUMBER:          144:429647
TITLE:                    PKB/AKT is involved in resumption of meiosis in mouse
                          oocytes
AUTHOR(S):                Kalous, Jaroslav; Solc, Petr; Baran, Vladimir;
                          Kubelka, Michal; Schultz, Richard M.; Motlik, Jan
CORPORATE SOURCE:         Institute of Animal Physiology and Genetics, Academy
                          of Sciences of the Czech Republic, Libechov, 277 21,
                          Czech Rep.
SOURCE:                   Biology of the Cell (2006), 98(2), 111-123
                          CODEN: BCELDF; ISSN: 0248-4900
PUBLISHER:                Portland Press Ltd.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   In fully grown mouse oocytes, a decrease in cAMP concentration precedes and is
     linked to CDK1 (cyclin-dependent kinase 1) activation. The mol. mechanism
     for this coupling, however, is not defined. PKB (protein kinase B, also
     called AKT) is implicated in CDK1 activation in lower species. During
     resumption of meiosis in starfish oocytes, MYT1, a neg. regulator of CDK1,
     is phosphorylated by PKB in an inhibitory manner. It can imply that PKB
     is also involved in CDK1 activation in mammalian oocytes. \Results. We
     monitored activation of PKB and CDK1 during maturation of mouse oocytes.
     PKB phosphorylation and activation preceded GVBD (germinal vesicle
     breakdown) in oocytes maturing either in vitro or in vivo. Activation was
     transient and PKB activity was markedly reduced when virtually all of the
     oocytes had undergone GVBD. PKB activation was
     independent of CDK1 activity, because although butyrolactone I prevented
     CDK1 activation and GVBD, PKB was nevertheless transiently phosphorylated
     and activated. LY-294002, an inhibitor of phosphoinositide 3-
     kinase-PKB signaling, suppressed activation of PKB and CDK1 as
     well as resumption of meiosis. OA (okadaic acid)-sensitive phosphatases
     are involved in PKB-activity regulation, because OA induced PKB
     hyperphosphorylation. During resumption of meiosis, PKB phosphorylated on
     Ser473 is associated with nuclear membrane and centrosome, whereas
     PKB phosphorylated on Thr308 is localized on centrosome only. Conclusions.
     The results of the present paper indicate that PKB is involved in CDK1
     activation and resumption of meiosis in mouse oocytes. The presence of
     phosphorylated PKB on centrosome at the time of GVBD suggests its
```

important role for an initial CDK1 activation.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 2 OF 15 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2005088955 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15718470
TITLE: Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex.
AUTHOR: Sarbassov D D; Guertin David A; Ali Siraj M; Sabatini David M
CORPORATE SOURCE: Whitehead Institute for Biomedical Research and Department of Biology, Massachusetts Institute of Technology, Nine Cambridge Center, Cambridge, MA 02142, USA.
CONTRACT NUMBER: R01 AI47389 (NIAID)
SOURCE: Science, (2005 Feb 18) Vol. 307, No. 5712, pp. 1098-101. Journal code: 0404511. E-ISSN: 1095-9203.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200503
ENTRY DATE: Entered STN: 19 Feb 2005
Last Updated on STN: 3 Mar 2005
Entered Medline: 2 Mar 2005
AB Deregulation of Akt/protein kinase B (PKB) is implicated in the pathogenesis of cancer and diabetes. Akt/PKB activation requires the phosphorylation of Thr308 in the activation loop by the phosphoinositide-dependent kinase 1 (PDK1) and Ser473 within the carboxyl-terminal hydrophobic motif by an unknown kinase. We show that in Drosophila and human cells the target of rapamycin (TOR) kinase and its associated protein rictor are necessary for Ser473 phosphorylation and that a reduction in rictor or mammalian TOR (mTOR) expression inhibited an Akt/PKB effector. The rictor-mTOR complex directly phosphorylated Akt/PKB on Ser473 in vitro and facilitated Thr308 phosphorylation by PDK1. Rictor-mTOR may serve as a drug target in tumors that have lost the expression of PTEN, a tumor suppressor that opposes Akt/PKB activation.

L22 ANSWER 3 OF 15 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2005516322 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16189199
TITLE: Developmental regulation of protein kinase B activation is isoform specific in skeletal muscle of neonatal pigs.
AUTHOR: Suryawan Agus; Davis Teresa A
CORPORATE SOURCE: USDA/ARS Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, Houston, Texas 77030, USA.
CONTRACT NUMBER: R01-AR44474 (NIAMS)
SOURCE: Pediatric research, (2005 Oct) Vol. 58, No. 4, pp. 719-24. Journal code: 0100714. ISSN: 0031-3998.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200601
ENTRY DATE: Entered STN: 29 Sep 2005
Last Updated on STN: 5 Jan 2006
Entered Medline: 4 Jan 2006
AB The postprandial activation of the insulin signaling pathway that leads to translation initiation is enhanced in skeletal muscle of the neonate and decreases with development in parallel with the developmental decline in muscle protein synthesis. Our previous study showed that the activity of protein kinase B (PKB), a major insulin signaling component, was higher in

7- than in 26-d-old pigs. To examine the molecular mechanisms involved, we determined PKB isoform abundance and phosphorylation state, the abundance of its kinases, and PKB's association with its kinases. The abundances of total PKB, PKBalpha, and PKBgamma were higher in muscle of 7- than in 26-d-old pigs whereas PKBbeta abundance was similar in the two age groups. PKB phosphorylation at Thr308 was higher in 7- than in 26-d-old pigs but PKB phosphorylation at Ser473 was similar in both age groups. The association of PKB with 3'-phosphoinositide -dependent kinase-1 (PDK-1), a kinase that phosphorylates PKB at Thr308, and PDK-1 abundance were higher in 7- than in 26-d-old pigs. Moreover, PDK-1 phosphorylation at Ser-241, a site that is crucial for PDK-1 activation, was higher in 7- than in 26-d-old pigs. However, the association of PKB with integrin-linked kinase (ILK), a kinase that potentially phosphorylates PKB at Ser473, and ILK abundance were similar in both age groups. The result suggests that the developmental change in PKB activation is isoform specific and involves regulation by PDK-1.

L22 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:630195 HCAPLUS
DOCUMENT NUMBER: 142:86015
TITLE: In vitro combination treatment with perifosine and UCN-01 demonstrates synergism against prostate (PC-3) and lung (A549) epithelial adenocarcinoma cell lines
AUTHOR(S): Dasmahapatra, Girija P.; Didolkar, Parijat; Alley, Michael C.; Ghosh, Somiranjan; Sausville, Edward A.; Roy, Krishnendu K.
CORPORATE SOURCE: Clinical Trials Unit, National Cancer Institute, Bethesda, MD, USA
SOURCE: Clinical Cancer Research (2004), 10(15), 5242-5252
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Antineoplastic agents often achieve antitumor activity at the expense of close to unacceptable toxicity. One potential avenue to improve therapeutic index might combine agents targeting distinct components of the same growth regulatory pathway. This might lead to more complete modulation of the target pathway at concns. lower than those associated with limiting adventitious toxicities from either agent alone. The protein kinase antagonist UCN-01 is currently used in Phase I/II trials and has recently been demonstrated to inhibit potently PDK1 (S. Sato et al., Oncogene, 21: 1727-1738, 2002). We have recently documented that the alkylphospholipid perifosine potently also inhibits Akt kinase (PKB) activation by interfering with membrane localization of Akt (S. Kondapaka et al., Mol. Cancer Ther., 2: 1093-1103, 2003). This leads to the hypothesis that these two agents might act synergistically through distinct mechanisms in the PI3K/Akt proliferation and survival-related signaling pathway. The synergistic effects of UCN-01 and perifosine, on two cell lines (A-549 and PC-3), were examined using various long-term in vitro assays for cell growth, cell cycle distribution, clonogenicity, survival morphol., and apo-ptosis. Along with Western blotting expts. were performed to determine whether this synergistic combination of two drugs has significant effect on their downstream targets and on biochem. markers of apoptosis. After 72 h, perifosine at concns. of 1.5 and 10 μM UCN-01 at 40 and 250 nM did not significantly affect the growth of PC-3 and A459 cells, resp. However, in combination at the same resp. individual concns. (1.5 μM and 40 nM of perifosine and UCN-01, resp., in PC-3 cells and 10 μM perifosine and 0.25 μM UCN-01 in the somewhat more resistant A549 cells), virtually complete growth inhibition of both the cell lines resulted. Supra-additive inhibition of growth was also demonstrated in independent clonogenic assays. Mechanistic studies in cell culture models suggest enhanced depletion of the S-phase population in cells treated by the

combination. This correlated with enhanced inactivation of Akt along with activation of caspases 3 and 9 and poly(ADP-ribose) polymerase cleavage. Evidence of synergy was formally demonstrated and occurred across a wide range of drug concns. and was largely independent of the order or sequence of drug addition As the concns. of UCN-01 and perifosine causing synergistic inhibition of cell growth are clin. achievable without prominent toxicity, these data support the development of clin. studies with this combination.
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 5 OF 15 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:287335 BIOSIS
DOCUMENT NUMBER: PREV200400286092
TITLE: Protein kinase B (PKB) activation decreases with development in skeletal muscle of neonatal pigs.
AUTHOR(S): Suryawan, Agus [Reprint Author]; Nguyen, Hanh; Orellana, Renan A; Liu, Chun W; Davis, Teresa A
CORPORATE SOURCE: Dept. of Pediatrics, Children &&AMP&N39; s Nutrition Research Center, Baylor College of Medicine, 1100 Bates Street, Houston, TX, 77030, USA
suryawan@bcm.tmc.edu
SOURCE: FASEB Journal, (2004) Vol. 18, No. 4-5, pp. Abst. 593.8. http://www.fasebj.org/. e-file.
Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. Washington, District of Columbia, USA. April 17-21, 2004. FASEB.
ISSN: 0892-6638 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jun 2004
Last Updated on STN: 16 Jun 2004
AB Postprandial activation of the insulin signaling pathway that leads to translation initiation is enhanced in skeletal muscle of the neonate and decreases with development in parallel with the developmental decline in muscle protein synthesis. Our previous study showed that the activity of PKB, a major insulin signaling component, was higher in 7- than in 26-d-old pigs. To examine possible molecular mechanisms, we determined PKB isoform abundance and phosphorylation state, the abundance of its kinases, and its association with its kinases. The abundances of total PKB, PKBalpha and PKBgamma were higher in muscle of 7- than 26-d-old pigs while PKBbeta abundance was similar. PKB phosphorylation at Thr308 was higher in 7- than 26-d-old pigs and phosphorylation at Ser473 was similar in both age groups. The association of PKB with 3&39;-phosphoinositide-dependent kinase-1 (PDK-1), a kinase that phosphorylates Thr308, and PDK-1 abundance were higher in 7- than 26-d-old pigs. However, the association of PKB with integrin-linked kinase (ILK), a kinase that potentially phosphorylates Ser473, and ILK abundance were similar in both age groups. Overall, the results suggest that the marked elevation in the abundances of PKBalpha and PDK-1 and the association of PKB-PDK-1 are likely responsible for the enhanced PKB activation in skeletal muscle of neonatal pigs.
Supported by NIH grants AR44474, USDA/ARS 6250-51000-031.

L22 ANSWER 6 OF 15 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:580025 SCISEARCH
THE GENUINE ARTICLE: 697YH
TITLE: Unravelling the activation mechanisms of protein kinase B/Akt
AUTHOR: Scheid M P; Woodgett J R (Reprint)
CORPORATE SOURCE: Ontario Canc Inst, 610 Univ Ave, Toronto, ON M5G 2M9, Canada (Reprint); Ontario Canc Inst, Toronto, ON M5G 2M9,

Canada
COUNTRY OF AUTHOR: Canada
SOURCE: FEBS LETTERS, (3 JUL 2003) Vol. 546, No. 1, pp. 108-112. ISSN: 0014-5793.
PUBLISHER: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 40
ENTRY DATE: Entered STN: 25 Jul 2003
Last Updated on STN: 25 Jul 2003
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Over the past decade, protein kinase B (PKB, also termed Akt) has emerged as an important signaling mediator between extracellular cues and modulation of gene expression, metabolism, and cell survival. The enzyme is tightly controlled and consequences of its deregulation include loss of growth control and oncogenesis. Recent work has better characterized the mechanism of PKB activation, including upstream regulators and secondary binding partners. This minireview refreshes some old concepts with new twists and highlights current outstanding questions. (C) 2003 Federation of European Biochemical Societies. Published by Elsevier Science B.V. All rights reserved.

L22 ANSWER 7 OF 15 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
DUPLICATE 3
ACCESSION NUMBER: 2002:287106 BIOSIS
DOCUMENT NUMBER: PREV200200287106
TITLE: Protein kinase B is regulated in platelets by the collagen receptor glycoprotein VI.
AUTHOR(S): Barry, Fiona A.; Gibbins, Jonathan M. [Reprint author]
CORPORATE SOURCE: School of Animal and Microbial Sciences, University of Reading, Whiteknights, Reading, RG6 6AJ, UK
j.m.gibbins@reading.ac.uk
SOURCE: Journal of Biological Chemistry, (April 12, 2002) Vol. 277, No. 15, pp. 12874-12878. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 8 May 2002
Last Updated on STN: 8 May 2002

AB Phosphoinositide 3-kinase (PI3K) is a critical component of the signaling pathways that control the activation of platelets. Here we have examined the regulation of protein kinase B (PKB), a downstream effector of PI3K, by the platelet collagen receptor glycoprotein (GP) VI and thrombin receptors. Stimulation of platelets with collagen or convulxin (a selective GPVI agonist) resulted in PI3K-dependent, and aggregation independent, Ser473 and Thr308 phosphorylation of PKBalpha, which results in PKB activation. This was accompanied by translocation of PKB to cell membranes. The phosphoinositide-dependent kinase PDK1 is known to phosphorylate PKBalpha on Thr308, although the identity of the kinase responsible for Ser473 phosphorylation is less clear. One candidate that has been implicated as being responsible for Ser473 phosphorylation, either directly or indirectly, is the integrin-linked kinase (ILK). In this study we have examined the interactions of PKB, PDK1, and ILK in resting and stimulated platelets. We demonstrate that in platelets PKB is physically associated with PDK1 and ILK. Furthermore, the association of PDK1 and ILK increases upon platelet stimulation. It would therefore appear that formation of a tertiary complex between PDK1, ILK, and PKB may be necessary for phosphorylation of PKB. These observations indicate that PKB participates in cell signaling downstream of the platelet collagen receptor GPVI. The role of PKB in collagen- and thrombin-stimulated platelets remains to be determined.

L22 ANSWER 8 OF 15 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2002496028 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12358757
TITLE: Activity-dependent NMDA receptor-mediated activation of protein kinase B/Akt in cortical neuronal cultures.
AUTHOR: Sutton Greg; Chandler L Judson
CORPORATE SOURCE: Department of Physiology and Neuroscience, Medical University of South Carolina, Charleston 29425, USA.
CONTRACT NUMBER: AA10983 (NIAAA)
SOURCE: Journal of neurochemistry, (2002 Sep) Vol. 82, No. 5, pp. 1097-105.
Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 3 Oct 2002
Last Updated on STN: 19 Oct 2002
Entered Medline: 18 Oct 2002

AB The serine/threonine protein kinase B (PKB)/Akt is a phosphoinositide 3-kinase (PI3K) effector that is thought to play an important roll in a wide variety of cellular events. The present study examined whether PKB activation in cortical neuronal cultures is coupled with synaptic activity. A 1-h incubation of neuronal cultures with tetrodotoxin (TTX), the PI3K inhibitor wortmannin, the NMDA receptor antagonist MK-801 or removal of extracellular calcium significantly reduced basal levels of phospho(Ser473)-PKB, indicating that activity-dependent glutamate release maintains PKB activation through an NMDA receptor-PI3K pathway. A 5-min exposure to NMDA (50 micro m) in the presence of TTX increased phospho-PKB back to levels observed in the absence of TTX. NMDA stimulation of phospho-PKB was blocked by wortmannin, the CaMKII inhibitor KN-93, MK-801, and removal of extracellular calcium. We have previously shown that NMDA receptors can bi-directionally regulate activation of extracellular-signal regulated kinase (ERK), and NMDA receptor stimulation of PKB in the present study appeared to mirror activation of ERK. These results suggest that in cultured cortical neurons, PKB activity is dynamically regulated by synaptic activity and is coupled to NMDA receptor activation. In addition, NMDA receptor activation of ERK and PKB may occur through overlapping signaling pathways that bifurcate at the level of Ras.

L22 ANSWER 9 OF 15 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 5
ACCESSION NUMBER: 2001:440059 BIOSIS
DOCUMENT NUMBER: PREV200100440059
TITLE: Chronic activation of atypical PKC-zeta in hyperglycemia-induced insulin resistance is associated with impaired Akt/PKB activation and decreased Ser473 but normal Thr308 phosphorylation: Evidence for a defect in a phosphoinositide-dependent kinase(PDK)-2.
AUTHOR(S): Bogdanovic, Elena [Reprint author]; Yu, Zhiwen [Reprint author]; Topic, Delilah [Reprint author]; Cho, Charles [Reprint author]; Fantus, I. George [Reprint author]
CORPORATE SOURCE: Toronto, ON, Canada
SOURCE: Diabetes, (June, 2001) Vol. 50, No. Supplement 2, pp. A267-A268. print.
Meeting Info.: 61st Scientific Sessions of the American Diabetes Association. Philadelphia, Pennsylvania, USA. June 22-26, 2001. American Diabetes Association.
CODEN: DIAEAZ. ISSN: 0012-1797.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Sep 2001
Last Updated on STN: 23 Feb 2002

L22 ANSWER 10 OF 15 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 6
ACCESSION NUMBER: 2000322232 EMBASE
TITLE: Dual regulation of platelet protein kinase B.
AUTHOR: Kroner C.; Eybrechts K.; Akkerman J.-W.N.
CORPORATE SOURCE: C. Kroner, Dept. of Haematology, Lab. for Thrombosis and Haemostasis, University Medical Center Utrecht, Heidelberglann 100, 3508 GA Utrecht, Netherlands. ckroner@lab.azu.nl
SOURCE: Journal of Biological Chemistry, (8 Sep 2000) Vol. 275, No. 36, pp. 27790-27798. .
Refs: 42
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 28 Sep 2000
Last Updated on STN: 28 Sep 2000

AB Protein kinase B (PKB) is a serine/threonine kinase that is activated by growth hormones and implicated in prevention of apoptosis, glycogen metabolism, and glucose uptake. A key enzyme in PKB activation is phosphatidylinositide 3-kinase (PI-3K), which triggers the dual phosphorylation of PKB by phosphatidylinositol-dependent kinases (PDKs). Here we report that the major PKB subtype in platelets is PKBα, which is activated by phosphorylation of Thr308 and Ser473 and has a constitutively phosphorylated Thr450 that does not contribute to PKB activation, α-Thrombin and thrombopoietin activate PKBα via PI-3K and trigger the concurrent phosphorylation of Thr308 (via PDK1) and Ser473 (via a not yet identified PDK2). In addition, α-thrombin activates a PI-3K-independent pathway involving phospholipase Cβ and calcium-dependent protein kinase C subtypes (PKCα/β). This route is specific for phosphorylation of Ser473 and can be initiated by direct PKC activation with phorbol ester or purified active PKC catalytic fragment in platelet lysate. Different degrees of Ser473 and Thr308 phosphorylation correlate with different degrees of enzyme activity. These data reveal a PI-3K-independent PKB activation in which PKCα/β regulates the phosphorylation of Ser473 in PKBα. The independent control of the two phosphorylation sites may contribute to fine regulation of PKBα activity.

L22 ANSWER 11 OF 15 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2000459945 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10958682
TITLE: 5' phospholipid phosphatase SHIP-2 causes protein kinase B inactivation and cell cycle arrest in glioblastoma cells.
AUTHOR: Taylor V; Wong M; Brandts C; Reilly L; Dean N M; Cowsert L M; Moodie S; Stokoe D
CORPORATE SOURCE: Cancer Research Institute, University of California, San Francisco 94115, USA.
CONTRACT NUMBER: R01CA79548 (NCI)
SOURCE: Molecular and cellular biology, (2000 Sep) Vol. 20, No. 18, pp. 6860-71.
Journal code: 8109087. ISSN: 0270-7306.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 5 Oct 2000
Last Updated on STN: 5 Oct 2000
Entered Medline: 22 Sep 2000

AB The tumor suppressor protein PTEN is mutated in glioblastoma multiform brain tumors, resulting in deregulated signaling through the phosphoinositide 3-kinase (PI3K)-protein kinase B (PKB) pathway, which is critical for maintaining proliferation and survival. We have examined the relative roles of the two major phospholipid products of PI3K activity, phosphatidylinositol 3,4-biphosphate [PtdIns(3,4)P2] and phosphatidylinositol 3,4,5-triphosphate [PtdIns(3,4,5)P3], in the regulation of PKB activity in glioblastoma cells containing high levels of both of these lipids due to defective PTEN expression. Reexpression of PTEN or treatment with the PI3K inhibitor LY294002 abolished the levels of both PtdIns(3, 4)P2 and PtdIns(3,4,5)P3, reduced phosphorylation of PKB on Thr308 and Ser473, and inhibited PKB activity. Overexpression of SHIP-2 abolished the levels of PtdIns(3,4,5)P3, whereas PtdIns(3,4)P2 levels remained high. However, PKB phosphorylation and activity were reduced to the same extent as they were with PTEN expression. PTEN and SHIP-2 also significantly decreased the amount of PKB associated with cell membranes. Reduction of SHIP-2 levels using antisense oligonucleotides increased PKB activity. SHIP-2 became tyrosine phosphorylated following stimulation by growth factors, but this did not significantly alter its phosphatase activity or ability to antagonize PKB activation. Finally we found that SHIP-2, like PTEN, caused a potent cell cycle arrest in G(1) in glioblastoma cells, which is associated with an increase in the stability of expression of the cell cycle inhibitor p27(KIP1). Our results suggest that SHIP-2 plays a negative role in regulating the PI3K-PKB pathway.

L22 ANSWER 12 OF 15 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 1999303798 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10373555
TITLE: Domain swapping used to investigate the mechanism of protein kinase B regulation by 3-phosphoinositide -dependent protein kinase 1 and Ser473 kinase.
AUTHOR: Andjelkovic M; Maira S M; Cron P; Parker P J; Hemmings B A
CORPORATE SOURCE: Friedrich Miescher-Institut, CH-4058 Basel, Switzerland.
SOURCE: Molecular and cellular biology, (1999 Jul) Vol. 19, No. 7, pp. 5061-72.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 30 Jul 1999
Last Updated on STN: 20 Apr 2002
Entered Medline: 22 Jul 1999

AB Protein kinase B (PKB or Akt), a downstream effector of phosphoinositide 3-kinase (PI 3-kinase), has been implicated in insulin signaling and cell survival. PKB is regulated by phosphorylation on Thr308 by 3-phosphoinositide-dependent protein kinase 1 (PDK1) and on Ser473 by an unidentified kinase. We have used chimeric molecules of PKB to define different steps in the activation mechanism. A chimera which allows inducible membrane translocation by lipid second messengers that activate in vivo protein kinase C and not PKB was created. Following membrane attachment, the PKB fusion protein was rapidly activated and

phosphorylated at the two key regulatory sites, Ser473 and Thr308, in the absence of further cell stimulation. This finding indicated that both PDK1 and the Ser473 kinase may be localized at the membrane of unstimulated cells, which was confirmed for PDK1 by immunofluorescence studies. Significantly, PI 3-kinase inhibitors prevent the phosphorylation of both regulatory sites of the membrane-targeted PKB chimera. Furthermore, we show that PKB activated at the membrane was rapidly dephosphorylated following inhibition of PI 3-kinase, with Ser473 being a better substrate for protein phosphatase. Overall, the results demonstrate that PKB is stringently regulated by signaling pathways that control both phosphorylation/activation and dephosphorylation/inactivation of this pivotal protein kinase.

L22 ANSWER 13 OF 15 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 1999382019 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10454216
TITLE: Mechanism of protein kinase B activation by insulin/insulin-like growth factor-1 revealed by specific inhibitors of phosphoinositide 3-kinase --significance for diabetes and cancer.
AUTHOR: Galetic I; Andjelkovic M; Meier R; Brodbeck D; Park J; Hemmings B A
CORPORATE SOURCE: Friedrich Miescher Institute, Basel, Switzerland.
SOURCE: Pharmacology & therapeutics, (1999 May-Jun) Vol. 82, No. 2-3, pp. 409-25. Ref: 198
Journal code: 7905840. ISSN: 0163-7258.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 11 Jan 2000
Last Updated on STN: 30 Jul 2001
Entered Medline: 26 Oct 1999

AB Protein kinase B (PKB) is a member of the second messenger subfamily of protein kinases. The three isoforms of PKB identified have an amino-terminal pleckstrin homology domain, a central kinase domain, and a carboxy-terminal regulatory domain. PKB is the major downstream target of receptor tyrosine kinases that signal via the phosphoinositide (PI) 3-kinase. The crucial role of lipid second messengers in PKB activation has been dissected through the use of the PI 3-kinase-specific inhibitors wortmannin and LY294002. Receptor-activated PI 3-kinase synthesises the lipid second messenger PI-3,4,5-trisphosphate, leading to the recruitment of PKB to the membrane. Membrane attachment of PKB is mediated by its pleckstrin homology domain binding to PI-3,4,5-trisphosphate or PI-3,4-bisphosphate with high affinity. Activation of PKB alpha and beta is then achieved at the plasma membrane by phosphorylation of Thr308/309 in the A-loop of the kinase domain and Ser473/474 in the carboxy-terminal regulatory region, respectively. The upstream kinase that phosphorylates PKB on Thr308, termed PI-dependent protein kinase-1, has been identified and extensively characterised. A candidate for the Ser473/474 kinase, termed the integrin-linked kinase, has been identified recently. Activated PKB is implicated in glucose metabolism, transcriptional control, and in the regulation of apoptosis in many different cell types. Stimulation of PKB activity protects cells from apoptosis by phosphorylation and inactivation of the pro-apoptotic protein BAD. These results could explain why PKB is overexpressed in some ovarian, breast, and pancreatic carcinomas.

L22 ANSWER 14 OF 15 MEDLINE on STN
ACCESSION NUMBER: 1999077797 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9857186

TITLE: Inactivation and dephosphorylation of protein kinase Balpha (PKBalpha) promoted by hyperosmotic stress.
AUTHOR: Meier R; Thelen M; Hemmings B A
CORPORATE SOURCE: Friedrich Miescher Institute, PO Box 2543, CH-4002 Basel, Switzerland.
SOURCE: The EMBO journal, (1998 Dec 15) Vol. 17, No. 24, pp. 7294-303.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 1 Mar 1999
Last Updated on STN: 20 Apr 2002
Entered Medline: 16 Feb 1999

AB To study the role of protein kinase B (PKB) in response to cellular stress, we examined PKBalpha activity following different stress treatments. Hyperosmotic but not chemical stress resulted in inactivation of PKBalpha and prevented activation by pervanadate and mitogens. Hyperosmotic shock did not affect the MAP kinase pathway, suggesting that this inhibitory effect was specific for PKB. Our data further indicate that downregulation occurs via dephosphorylation of Thr308 and Ser473, the major regulatory phosphorylation sites of PKBalpha. Indeed, calyculin A, which inhibits protein phosphatases 1 and 2A, effectively blocked hyperosmotic stress-mediated inactivation (dephosphorylation) of PKBalpha. High osmolarity did not affect phosphatidylinositol 3-kinase activity but led to a marked increase in PI(3,4,5)P3 and a decrease in PI(3,4)P2 formation after pervanadate stimulation, suggesting that hyperosmotic stress has an inhibitory effect on a phosphatidylinositol 5-phosphatase which converts PI(3,4,5)P3 into PI(3,4)P2. Immunofluorescence studies revealed that membrane translocation, a prerequisite for PKB activation, was not affected by hyperosmotic stress. Our results indicate that hyperosmotic stress can act at two levels: (i) inhibition of phosphorylation of Thr308 and Ser473 by upstream kinases and (ii) by promoting rapid dephosphorylation of these regulatory sites.

L22 ANSWER 15 OF 15 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 1998058941 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9395488
TITLE: Role of translocation in the activation and function of protein kinase B.
AUTHOR: Andjelkovic M; Alessi D R; Meier R; Fernandez A; Lamb N J; Frech M; Cron P; Cohen P; Lucocq J M; Hemmings B A
CORPORATE SOURCE: Friedrich Miescher-Institut, Maulbeerstrasse 66, CH-4056 Basel, Switzerland.
SOURCE: The Journal of biological chemistry, (1997 Dec 12) Vol. 272, No. 50, pp. 31515-24.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 29 Jan 1998
Last Updated on STN: 19 Dec 2002
Entered Medline: 15 Jan 1998

AB We have investigated the role of subcellular localization in the regulation of protein kinase B (PKB) activation. The myristoylation/palmitylation motif from the Lck tyrosine kinase was attached to the N terminus of protein kinase B to alter its subcellular location. Myristoylated/palmitylated (m/p)-PKBalpha was associated with the plasma membrane of transfected cells, whereas the wild-type kinase was

mostly cytosolic. The activity of m/p-PKBalpha was 60-fold higher compared with the unstimulated wild-type enzyme, and could not be stimulated further by growth factors or phosphatase inhibitors. In vivo 32P labeling and mutagenesis demonstrated that m/p-PKBalpha activity was due to phosphorylation on Thr308 and Ser473, that are normally induced on PKB following stimulation of the cells with insulin or insulin-like growth factor-1 (IGF-1). A dominant negative form of phosphoinositide 3-kinase (PI3-K) did not affect m/p-PKBalpha activity. The pleckstrin homology (PH) domain of m/p-PKBalpha was not required for its activation or phosphorylation on Thr308 and Ser473, suggesting that this domain may serve as a membrane-targeting module. Consistent with this view, PKBalpha was translocated to the plasma membrane within minutes after stimulation with IGF-1. This translocation required the PH domain and was sensitive to wortmannin. Our results indicate that PI3-K activity is required for translocation of PKB to the plasma membrane, where its activation occurs through phosphorylation of the same sites that are induced by insulin or IGF-1. Following activation the kinase detached from the membrane and translocated to the nucleus.

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=> d his

     (FILE 'HOME' ENTERED AT 10:08:25 ON 28 JUL 2006)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 10:08:53 ON 28 JUL 2006
L1         67106 S PHOSPHOINOSITIDE
L2         19704 S L1 (2W) KINASE##
L3          2205 S PDK1
L4         20665 S L2 OR L3
L5           319 S PRK2
L6            60 S L4 AND L5
L7            27 DUP REM L6 (33 DUPLICATES REMOVED)
L8            12 S L5 AND PIF
L9             3 DUP REM L8 (9 DUPLICATES REMOVED)
L10          346 S PKC (W)RELATED
L11           43 S L5 AND L10
L12           31 DUP REM L11 (12 DUPLICATES REMOVED)
L13           18 S PDK2 AND L5
L14            8 DUP REM L13 (10 DUPLICATES REMOVED)
L15         1023 S PKB (W)ACTIVAT?
L16           72 S L3 AND L15
L17           19 DUP REM L16 (53 DUPLICATES REMOVED)
L18            0 S L5 AND L15
L19          248 S L4 AND L15
L20         1092 S SER473
L21           43 S L19 AND L20
L22           15 DUP REM L21 (28 DUPLICATES REMOVED)

=> e alessi d/au
E1             2     ALESSI CRISTIANE R/AU
E2             1     ALESSI CRISTIANE RODRIGUES/AU
E3           138 --> ALESSI D/AU
E4             2     ALESSI D A/AU
E5             2     ALESSI D E/AU
E6             1     ALESSI D F/AU
E7             1     ALESSI D L/AU
E8            73     ALESSI D M/AU
E9             4     ALESSI D P/AU
E10          337     ALESSI D R/AU
E11            3     ALESSI D S/AU
E12            4     ALESSI DANIEL/AU
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=> s e3
L23         138 "ALESSI D"/AU

=> e balendran a/au
E1           79     BALENDRA T/AU
E2            2     BALENDRA W/AU
E3           30 --> BALENDRAN A/AU
E4            1     BALENDRAN ANU/AU
E5           15     BALENDRAN ANUDHARAN/AU
E6            1     BALENDRAN ANUSHA/AU
E7            8     BALENDRAN B/AU
E8            3     BALENDRAN C/AU
E9            3     BALENDRAN CLARE/AU
E10          22     BALENDRAN N/AU
E11           4     BALENDRAN NALINI/AU
E12          15     BALENDRAN P/AU

=> s e3-e6
L24          47 ("BALENDRAN A"/AU OR "BALENDRAN ANU"/AU OR "BALENDRAN ANUDHARAN"
                /AU OR "BALENDRAN ANUSHA"/AU)

=> e deak m/au
E1            5     DEAK LINDA/AU
E2            1     DEAK LR/AU
E3          194 --> DEAK M/AU
E4           13     DEAK M A/AU
E5            7     DEAK M M/AU
E6           13     DEAK M R/AU
E7            1     DEAK MAGDOLNA/AU
E8          153     DEAK MARIA/AU
E9            1     DEAK MARTIN/AU
E10           2     DEAK MARY ROSE/AU
E11           1     DEAK MARYANN C/AU
E12           1     DEAK MIHAIL/AU

=> s e3
L25         194 "DEAK M"/AU

=> e currie r/au
E1            1     CURRIE PHILLIP/AU
E2            1     CURRIE PHILLIP J/AU
E3          105 --> CURRIE R/AU
E4          155     CURRIE R A/AU
E5            2     CURRIE R A */AU
E6           33     CURRIE R ALEXANDER/AU
E7           25     CURRIE R B/AU
E8            5     CURRIE R C/AU
E9           10     CURRIE R D/AU
E10           1     CURRIE R E/AU
E11          14     CURRIE R F/AU
E12          85     CURRIE R G/AU

=> s e3
L26         105 "CURRIE R"/AU

=> e downes p/au
E1            3     DOWNES NINA/AU
E2            1     DOWNES NOEL/AU
E3           30 --> DOWNES P/AU
E4           11     DOWNES P C/AU
E5            4     DOWNES P J/AU
E6           22     DOWNES P K/AU
E7            6     DOWNES P M/AU
E8            2     DOWNES P S/AU
```

```
E9            1      DOWNES P T/AU
E10           3      DOWNES PATRICK/AU
E11           1      DOWNES PAUL/AU
E12           1      DOWNES PETE/AU

=> s e3
L27          30 "DOWNES P"/AU

=> e casamayor a/au
E1            1      CASAMAYO J/AU
E2            1      CASAMAYOR/AU
E3          111 --> CASAMAYOR A/AU
E4            1      CASAMAYOR A J/AU
E5           60      CASAMAYOR ANTONIO/AU
E6            1      CASAMAYOR ANTONIO J/AU
E7            1      CASAMAYOR C/AU
E8            1      CASAMAYOR DAUDINOT R/AU
E9           12      CASAMAYOR DEL CACHO M/AU
E10           1      CASAMAYOR DUADINET R/AU
E11           1      CASAMAYOR E/AU
E12          81      CASAMAYOR E O/AU

=> s e3
L28         111 "CASAMAYOR A"/AU

=> d his

     (FILE 'HOME' ENTERED AT 10:08:25 ON 28 JUL 2006)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 10:08:53 ON 28 JUL 2006
L1         67106 S PHOSPHOINOSITIDE
L2         19704 S L1 (2W) KINASE##
L3          2205 S PDK1
L4         20665 S L2 OR L3
L5           319 S PRK2
L6            60 S L4 AND L5
L7            27 DUP REM L6 (33 DUPLICATES REMOVED)
L8            12 S L5 AND PIF
L9             3 DUP REM L8 (9 DUPLICATES REMOVED)
L10          346 S PKC (W)RELATED
L11           43 S L5 AND L10
L12           31 DUP REM L11 (12 DUPLICATES REMOVED)
L13           18 S PDK2 AND L5
L14            8 DUP REM L13 (10 DUPLICATES REMOVED)
L15         1023 S PKB (W)ACTIVAT?
L16           72 S L3 AND L15
L17           19 DUP REM L16 (53 DUPLICATES REMOVED)
L18            0 S L5 AND L15
L19          248 S L4 AND L15
L20         1092 S SER473
L21           43 S L19 AND L20
L22           15 DUP REM L21 (28 DUPLICATES REMOVED)
                 E ALESSI D/AU
L23          138 S E3
                 E BALENDRAN A/AU
L24           47 S E3-E6
                 E DEAK M/AU
L25          194 S E3
                 E CURRIE R/AU
L26          105 S E3
                 E DOWNES P/AU
L27           30 S E3
                 E CASAMAYOR A/AU
```

```
L28          111 S E3

=> s l23 or l24 or l25 or l26 or l27
L29          496 L23 OR L24 OR L25 OR L26 OR L27

=> sd his
SD IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d his

     (FILE 'HOME' ENTERED AT 10:08:25 ON 28 JUL 2006)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 10:08:53 ON 28 JUL 2006
L1         67106 S PHOSPHOINOSITIDE
L2         19704 S L1 (2W) KINASE##
L3          2205 S PDK1
L4         20665 S L2 OR L3
L5           319 S PRK2
L6            60 S L4 AND L5
L7            27 DUP REM L6 (33 DUPLICATES REMOVED)
L8            12 S L5 AND PIF
L9             3 DUP REM L8 (9 DUPLICATES REMOVED)
L10          346 S PKC (W)RELATED
L11           43 S L5 AND L10
L12           31 DUP REM L11 (12 DUPLICATES REMOVED)
L13           18 S PDK2 AND L5
L14            8 DUP REM L13 (10 DUPLICATES REMOVED)
L15         1023 S PKB (W)ACTIVAT?
L16           72 S L3 AND L15
L17           19 DUP REM L16 (53 DUPLICATES REMOVED)
L18            0 S L5 AND L15
L19          248 S L4 AND L15
L20         1092 S SER473
L21           43 S L19 AND L20
L22           15 DUP REM L21 (28 DUPLICATES REMOVED)
               E ALESSI D/AU
L23          138 S E3
               E BALENDRAN A/AU
L24           47 S E3-E6
               E DEAK M/AU
L25          194 S E3
               E CURRIE R/AU
L26          105 S E3
               E DOWNES P/AU
L27           30 S E3
               E CASAMAYOR A/AU
L28          111 S E3
L29          496 S L23 OR L24 OR L25 OR L26 OR L27

=> s l7 and l29
L30           5 L7 AND L29

=> dup rem l30
PROCESSING COMPLETED FOR L30
L31           5 DUP REM L30 (0 DUPLICATES REMOVED)

=> d 1-5 ibib ab

L31  ANSWER 1 OF 5  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2000:688348  HCAPLUS
```

DOCUMENT NUMBER: 133:278041
TITLE: Altered specificity of phosphoinositide -dependent protein kinase PDK1 in presence of substrate consensus peptides
INVENTOR(S): Alessi, Dario; Balendran, Anudharan; Deak, Maria; Currie, Richard; Downes, Peter; Casamayor, Antonio
PATENT ASSIGNEE(S): University of Dundee, UK
SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000056864	A2	20000928	WO 2000-GB1004	20000317
WO 2000056864	A3	20010118		
W: JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1165761	A2	20020102	EP 2000-911069	20000317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002539780	T2	20021126	JP 2000-606723	20000317
PRIORITY APPLN. INFO.:			GB 1999-6245 A	19990319
			WO 2000-GB1004 W	20000317

OTHER SOURCE(S): MARPAT 133:278041

AB A method of altering the substrate specificity of phosphoinositide -dependent protein kinase 1 (PDK1) is provided, wherein the said PDK1 is exposed to a polypeptide which comprises the amino acid sequence Phe/Tyr-Xaa-Xaa-Phe/Tyr-Zaa-Phe/Tyr wherein Zaa represents a neg. charged amino acid residue. The PDK1 with altered substrate specificity is capable of phosphorylating the Ser/Thr residue in a polypeptide with an amino acid sequence corresponding to the consensus sequence Phe/Tyr-Xaa-Xaa-Phe/Tyr-Ser/Thr-Phe/Tyr. The PDK1 with altered specificity may be useful in screening assays and for phosphorylating substrates having the above consensus sequence.

L31 ANSWER 2 OF 5 MEDLINE on STN
ACCESSION NUMBER: 2000396616 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10764742
TITLE: A 3-phosphoinositide-dependent protein kinase-1 (PDK1) docking site is required for the phosphorylation of protein kinase Czeta (PKCzeta) and PKC-related kinase 2 by PDK1.
AUTHOR: Balendran A; Biondi R M; Cheung P C; Casamayor A; Deak M; Alessi D R
CORPORATE SOURCE: MRC Protein Phosphorylation Unit, Division of Signal Transduction Therapy, MSI/WTB Complex, University of Dundee, Dow Street, Dundee DD1 5EH, Scotland, United Kingdom.
SOURCE: The Journal of biological chemistry, (2000 Jul 7) Vol. 275, No. 27, pp. 20806-13.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 24 Aug 2000
Last Updated on STN: 20 Apr 2002

Entered Medline: 16 Aug 2000

AB Members of the AGC subfamily of protein kinases including protein kinase B, p70 S6 kinase, and protein kinase C (PKC) isoforms are activated and/or stabilized by phosphorylation of two residues, one that resides in the T-loop of the kinase domain and the other that is located C-terminal to the kinase domain in a region known as the hydrophobic motif. Atypical PKC isoforms, such as PKCzeta, and the PKC-related kinases, like PRK2, are also activated by phosphorylation of their T-loop site but, instead of possessing a phosphorylatable Ser/Thr in their hydrophobic motif, contain an acidic residue. The 3-phosphoinositide -dependent protein kinase (PDK1) activates many members of the AGC subfamily of kinases in vitro, including PKCzeta and PRK2 by phosphorylating the T-loop residue. In the present study we demonstrate that the hydrophobic motifs of PKCzeta and PKCiota, as well as PRK1 and PRK2, interact with the kinase domain of PDK1. Mutation of the conserved residues of the hydrophobic motif of full-length PKCzeta, full-length PRK2, or PRK2 lacking its N-terminal regulatory domain abolishes or significantly reduces the ability of these kinases to interact with PDK1 and to become phosphorylated at their T-loop sites in vivo. Furthermore, overexpression of the hydrophobic motif of PRK2 in cells prevents the T-loop phosphorylation and thus inhibits the activation of PRK2 and PKCzeta. These findings indicate that the hydrophobic motif of PRK2 and PKCzeta acts as a "docking site" enabling the recruitment of PDK1 to these substrates. This is essential for their phosphorylation by PDK1 in cells.

L31 ANSWER 3 OF 5 MEDLINE on STN
ACCESSION NUMBER: 2000164465 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10698939
TITLE: Identification of a pocket in the PDK1 kinase domain that interacts with PIF and the C-terminal residues of PKA.
AUTHOR: Biondi R M; Cheung P C; Casamayor A; Deak M; Currie R A; Alessi D R
CORPORATE SOURCE: Divison of Signal Transduction Therapy, MSI/WTB Complex, University of Dundee, Dow Street, Dundee DD1 5EH, UK.. rbiondi@bad.dundee.ac.uk
SOURCE: The EMBO journal, (2000 Mar 1) Vol. 19, No. 5, pp. 979-88. Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 5 May 2000
Last Updated on STN: 20 Apr 2002
Entered Medline: 26 Apr 2000

AB The 3-phosphoinositide-dependent protein kinase-1 (PDK1) phosphorylates and activates a number of protein kinases of the AGC subfamily. The kinase domain of PDK1 interacts with a region of protein kinase C-related kinase-2 (PRK2), termed the PDK1-interacting fragment (PIF), through a hydrophobic motif. Here we identify a hydrophobic pocket in the small lobe of the PDK1 kinase domain, separate from the ATP- and substrate-binding sites, that interacts with PIF. Mutation of residues predicted to form part of this hydrophobic pocket either abolished or significantly diminished the affinity of PDK1 for PIF. PIF increased the rate at which PDK1 phosphorylated a synthetic dodecapeptide (T308tide), corresponding to the sequences surrounding the PDK1 phosphorylation site of PKB. This peptide is a poor substrate for PDK1, but a peptide comprising T308tide fused to the PDK1 -binding motif of PIF was a vastly superior substrate for PDK1. Our results suggest that the PIF-binding pocket on the kinase domain of

PDK1 acts as a 'docking site', enabling it to interact with and enhance the phosphorylation of its substrates.

L31 ANSWER 4 OF 5 MEDLINE on STN
ACCESSION NUMBER: 2001061082 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11078882
TITLE: Further evidence that 3-phosphoinositide -dependent protein kinase-1 (PDK1) is required for the stability and phosphorylation of protein kinase C (PKC) isoforms.
AUTHOR: Balendran A; Hare G R; Kieloch A; Williams M R; Alessi D R
CORPORATE SOURCE: MRC Protein Phosphorylation, MSI/WTB complex, University of Dundee, Dow Street, DD1 5EH, Dundee, UK.
SOURCE: FEBS letters, (2000 Nov 10) Vol. 484, No. 3, pp. 217-23. Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 20 Apr 2002
Entered Medline: 22 Dec 2000

AB The multi-site phosphorylation of the protein kinase C (PKC) superfamily plays an important role in the regulation of these enzymes. One of the key phosphorylation sites required for the activation of all PKC isoforms lies in the T-loop of the kinase domain. Recent in vitro and transfection experiments indicate that phosphorylation of this residue can be mediated by the 3-phosphoinositide-dependent protein kinase-1 (PDK1). In this study, we demonstrate that in embryonic stem (ES) cells lacking PDK1 (PDK1-/- cells), the intracellular levels of endogenously expressed PKCalpha, PKCbetaI, PKCgamma, PKCdelta, PKCepsilon, and PKC-related kinase-1 (PRK1) are vastly reduced compared to control ES cells (PDK1+/+ cells). The levels of PKCzeta and PRK2 protein are only moderately reduced in the PDK1-/- ES cells. We demonstrate that in contrast to PKCzeta expressed PDK1+/+ ES cells, PKCzeta in ES cells lacking PDK1 is not phosphorylated at its T-loop residue. This provides the first genetic evidence that PKCzeta is a physiological substrate for PDK1. In contrast, PRK2 is still partially phosphorylated at its T-loop in PDK1-/- cells, indicating the existence of a PDK1 -independent mechanism for the phosphorylation of PRK2 at this residue.

L31 ANSWER 5 OF 5 MEDLINE on STN
ACCESSION NUMBER: 1999244939 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10226025
TITLE: PDK1 acquires PDK2 activity in the presence of a synthetic peptide derived from the carboxyl terminus of PRK2.
AUTHOR: Balendran A; Casamayor A; Deak M; Paterson A; Gaffney P; Currie R; Downes C P; Alessi D R
CORPORATE SOURCE: MRC Protein Phosphorylation Unit, Department of Biochemistry, University of Dundee, Dundee DD1 5EH, UK.
SOURCE: Current biology : CB, (1999 Apr 22) Vol. 9, No. 8, pp. 393-404. Journal code: 9107782. ISSN: 0960-9822.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906

ENTRY DATE: Entered STN: 14 Jun 1999
Last Updated on STN: 20 Apr 2002
Entered Medline: 1 Jun 1999

AB BACKGROUND: Protein kinase B (PKB) is activated by phosphorylation of Thr308 and of Ser473. Thr308 is phosphorylated by the 3-phosphoinositide-dependent protein kinase-1 (PDK1) but the identity of the kinase that phosphorylates Ser473 (provisionally termed PDK2) is unknown. RESULTS: The kinase domain of PDK1 interacts with a region of protein kinase C-related kinase-2 (PRK2), termed the PDK1-interacting fragment (PIF). PIF is situated carboxy-terminal to the kinase domain of PRK2, and contains a consensus motif for phosphorylation by PDK2 similar to that found in PKBalpha, except that the residue equivalent to Ser473 is aspartic acid. Mutation of any of the conserved residues in the PDK2 motif of PIF prevented interaction of PIF with PDK1. Remarkably, interaction of PDK1 with PIF, or with a synthetic peptide encompassing the PDK2 consensus sequence of PIF, converted PDK1 from an enzyme that could phosphorylate only Thr308 of PKBalpha to one that phosphorylates both Thr308 and Ser473 of PKBalpha in a manner dependent on phosphatidylinositol (3,4,5) trisphosphate (PtdIns(3,4,5)P3). Furthermore, the interaction of PIF with PDK1 converted the PDK1 from a form that is not directly activated by PtdIns(3,4,5)P3 to a form that is activated threefold by PtdIns(3,4,5)P3. We have partially purified a kinase from brain extract that phosphorylates Ser473 of PKBalpha in a PtdIns(3,4,5)P3-dependent manner and that is immunoprecipitated with PDK1 antibodies. CONCLUSIONS: PDK1 and PDK2 might be the same enzyme, the substrate specificity and activity of PDK1 being regulated through its interaction with another protein(s). PRK2 is a probable substrate for PDK1.

=> d his

(FILE 'HOME' ENTERED AT 10:08:25 ON 28 JUL 2006)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 10:08:53 ON 28 JUL 2006

L1 67106 S PHOSPHOINOSITIDE
L2 19704 S L1 (2W) KINASE##
L3 2205 S PDK1
L4 20665 S L2 OR L3
L5 319 S PRK2
L6 60 S L4 AND L5
L7 27 DUP REM L6 (33 DUPLICATES REMOVED)
L8 12 S L5 AND PIF
L9 3 DUP REM L8 (9 DUPLICATES REMOVED)
L10 346 S PKC (W)RELATED
L11 43 S L5 AND L10
L12 31 DUP REM L11 (12 DUPLICATES REMOVED)
L13 18 S PDK2 AND L5
L14 8 DUP REM L13 (10 DUPLICATES REMOVED)
L15 1023 S PKB (W)ACTIVAT?
L16 72 S L3 AND L15
L17 19 DUP REM L16 (53 DUPLICATES REMOVED)
L18 0 S L5 AND L15
L19 248 S L4 AND L15
L20 1092 S SER473
L21 43 S L19 AND L20
L22 15 DUP REM L21 (28 DUPLICATES REMOVED)
E ALESSI D/AU
L23 138 S E3
E BALENDRAN A/AU
L24 47 S E3-E6

```
                E DEAK M/AU
L25         194 S E3
                E CURRIE R/AU
L26         105 S E3
                E DOWNES P/AU
L27          30 S E3
                E CASAMAYOR A/AU
L28         111 S E3
L29         496 S L23 OR L24 OR L25 OR L26 OR L27
L30           5 S L7 AND L29
L31           5 DUP REM L30 (0 DUPLICATES REMOVED)
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	L #	Hits	Search Text
1	L1	279	PDK1
2	L2	616	phosphoinositide adj2 kinase$2
3	L3	817	l1 or l2
4	L4	248	PRK2
5	L5	26	l3 same l4
6	L6	1504	PKB or ser473
7	L7	26	l4 same l6
8	L8	4987	ALESS IBALENDRAN DEAK CURRIE CASAMAYOR
9	L9	10	l5 and l8
10	L10	8	l7 and l8

	Issue Date	Pages	Document ID	Title
1	20060504	38	US 20060094059 A1	Methods for identifying new drug leads and new therapeutic uses for known drugs
2	20060413	49	US 20060079494 A1	Specific kinase inhibitors
3	20060330	144	US 20060068414 A1	Identification of aging genes through large-scale analysis
4	20060223	27	US 20060040338 A1	Pharmacological profiling of drugs with cell-based assays
5	20060216	92	US 20060035898 A1	Fused ring heterocycle kinase modulators
6	20060209	155	US 20060030583 A1	Pyrrolo-pyridine kinase modulators
7	20060105	171	US 20060004052 A1	Tricyclic compounds protein kinase inhibitors for enhancing the efficacy of anti-neoplastic agents and radiation therapy
8	20060105	132	US 20060004043 A1	Indazole compounds and methods of use thereof
9	20051208	24	US 20050272708 A1	Akt inhibitors, pharmaceutical compositions, and uses thereof
10	20051027	40	US 20050239110 A1	Method of diagnosing depression
11	20051020	13	US 20050232804 A1	Metal alloy and metal alloy storage product for storing radioactive materials
12	20050922	72	US 20050209176 A1	Compounds that interact with kinases

	Issue Date	Pages	Document ID	Title
13	20050707	58	US 20050148643 A1	Carbamate compositions and methods fo rmodulating the activity of the CHK1 enzyme
14	20050707	21	US 20050148031 A1	Catalytic efficiency and/or specificity of non-native substrates of enzymes
15	20050519	57	US 20050107386 A1	Methods of treating diseases and disorders by targeting multiple kinases
16	20050407	176	US 20050075499 A1	Tricyclic compounds protein kinase inhibitors for enhancing the efficacy of anti-neoplastic agents and radiation therapy
17	20050224	62	US 20050043381 A1	Aminopyrazole compounds
18	20050120	27	US 20050014682 A1	Cell-free assay for insulin signaling
19	20050113	240	US 20050009876 A1	Indazole compounds, compositions thereof and methods of treatment therewith
20	20040115	176	US 20040009569 A1	Kinase crystal structures and materials and methods for kinase activation
21	20040108	134	US 20040005687 A1	Kinase crystal structures
22	20030731	38	US 20030144204 A1	Akt-based inducible survival switch

23	20030731	90	US 2003014365 6 A1	Protein kinase regulation

	Issue Date	Pages	Document ID	Title
24	20020815	170	US 20020110811 A1	Variants of protein kinases
25	20051122	163	US 6967198 B2	Tricyclic compounds protein kinase inhibitors for enhancing the efficacy of anti-neoplastic agents and radiation therapy
26	20050830	166	US 6936450 B2	Variants of protein kinases

	Issue Date	Pages	Document ID	Title
1	20060713	36	US 20060154961 A1	Thiadiazole compounds and methods of use
2	20060330	144	US 20060068414 A1	Identification of aging genes through large-scale analysis
3	20060223	27	US 20060040338 A1	Pharmacological profiling of drugs with cell-based assays
4	20060216	92	US 20060035898 A1	Fused ring heterocycle kinase modulators
5	20060209	155	US 20060030583 A1	Pyrrolo-pyridine kinase modulators
6	20060105	171	US 20060004052 A1	Tricyclic compounds protein kinase inhibitors for enhancing the efficacy of anti-neoplastic agents and radiation therapy
7	20060105	135	US 20060003968 A1	Azaindoles useful as inhibitors of rock and other protein kinases
8	20051020	13	US 20050232804 A1	Metal alloy and metal alloy storage product for storing radioactive materials
9	20050707	58	US 20050148643 A1	Carbamate compositions and methods fo rmodulating the activity of the CHK1 enzyme
10	20050407	176	US 20050075499 A1	Tricyclic compounds protein kinase inhibitors for enhancing the efficacy of anti-neoplastic agents and radiation therapy
11	20050224	62	US 20050043381 A1	Aminopyrazole compounds

12	20041223	40	US 2004025908 6 A1	Novel genes, compositions, kits, and methods for identification, assessment, prevention, and therapy of human prostate cancer

	Issue Date	Pages	Document ID	Title
13	20040115	176	US 20040009569 A1	Kinase crystal structures and materials and methods for kinase activation
14	20040115	131	US 20040009481 A1	Compositions, kits, and methods for identification, assessment, prevention, and therapy of human prostate cancer
15	20040108	134	US 20040005687 A1	Kinase crystal structures
16	20030904	38	US 20030165831 A1	Novel genes, compositions, kits, and methods for identification, assessment, prevention, and therapy of ovarian cancer
17	20030731	90	US 20030143656 A1	Protein kinase regulation
18	20030724	44	US 20030138792 A1	Compositions, kits, and methods for identification, assessment, prevention and therapy of cervical cancer
19	20030529	36	US 20030099974 A1	Novel genes, compositions, kits and methods for identification, assessment, prevention, and therapy of breast cancer
20	20030102	47	US 20030003479 A1	Compositions, kits, and methods for identification, assessment, prevention, and therapy of ovarian cancer
21	20021205	56	US 20020182619 A1	Compositions, kits, and methods for identification, assessment, prevention, and therapy of ovarian cancer

	Issue Date	Pages	Document ID	Title
22	20021114	506	US 20020168638 A1	Compositions, kits, and methods for identification, assessment, prevention, and therapy of human prostate cancer
23	20020815	170	US 20020110811 A1	Variants of protein kinases
24	20020124	41	US 20020009724 A1	Compositions, kits, and methods for identification, assessment, prevention, and therapy of cervical cancer
25	20051122	163	US 6967198 B2	Tricyclic compounds protein kinase inhibitors for enhancing the efficacy of anti-neoplastic agents and radiation therapy
26	20050830	166	US 6936450 B2	Variants of protein kinases

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1	20060105	171	US 20060004052 A1	Tricyclic compounds protein kinase inhibitors for enhancing the efficacy of anti-neoplastic agents and radiation therapy
2	20050707	58	US 20050148643 A1	Carbamate compositions and methods fo rmodulating the activity of the CHK1 enzyme
3	20050707	21	US 20050148031 A1	Catalytic efficiency and/or specificity of non-native substrates of enzymes
4	20050407	176	US 20050075499 A1	Tricyclic compounds protein kinase inhibitors for enhancing the efficacy of anti-neoplastic agents and radiation therapy
5	20050224	62	US 20050043381 A1	Aminopyrazole compounds
6	20050120	27	US 20050014682 A1	Cell-free assay for insulin signaling
7	20040115	176	US 20040009569 A1	Kinase crystal structures and materials and methods for kinase activation
8	20040108	134	US 20040005687 A1	Kinase crystal structures
9	20030731	90	US 20030143656 A1	Protein kinase regulation

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